b]oxazol-2-ylmethyl)piperazin-1-yl]acetate

^{1}H-NMR ($CDCl_3$) δppm:

1.25 (3H, t, J = 7.1 Hz), 1.60 (3H, s), 2.45 - 2.64 (6H, m), 2.55 (1H, d, J = 14.8 Hz), 2.72 - 2.81 (2H, m), 2.87 (1H, d, J = 14.8 Hz), 3.14 (2H, s), 3.90 (1H, d, J = 9.7 Hz), 4.16 (2H, q, J = 7.1 Hz), 4.31 (1H, d, J = 9.7 Hz), 7.57 (1H, s).

Example 335

3-{3-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]propyl}-3H-benzoxazol-2-one

Melting point 123-126°C.

Example 336

1-(4-Chlorophenyl)-2-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone

^{1}H-NMR ($CDCl_3$) δppm:

1.60 (3H, s), 2.47 (4H, br), 2.53 (1H, d, J = 14.9 Hz), 2.57 - 2.65 (2H, m), 2.74 - 2.84 (2H, m), 2.87 (1H, d, J = 14.9 Hz), 3.64 (1H, d, J = 16.7 Hz), 3.75 (1H, d, J = 16.7 Hz), 3.90 (1H, d, J = 9.7 Hz), 4.30 (1H, d, J = 9.7 Hz), 7.42 (2H, d, J = 8.6 Hz), 7.54 (1H, s), 7.92 (2H, d, J = 8.6 Hz).

Example 337

Preparation of benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

A mixture of 2-(4-tert-butoxycarbonyl-

piperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 306 (130 mg, 0.35 mmol), trifluoroacetic acid (3 ml) and methylene chloride (5 ml) was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (5 ml) and added triethylamine (107.5 mg, 1.06 mmol). To the solution, benzyl chloroformate (120 mg, 0.71 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 1 hour. The reaction mixture was washed with water, a saturated sodium hydrogencarbonate solution and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford a yellow oil. The oil was dissolved in ethyl acetate (5 ml). To the solution, a saturated hydrochloride solution in ethyl acetate was added, and the precipitates were filtered off to afford benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-carboxylate hydrochloride (46.8 mg, yield 30%) as a white powder.

Melting point 130.5-132.1°C.

Using corresponding starting materials gave compounds of Examples 338 to 340 in the same manner as in Example 337.

Example 338

Phenyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Melting point 81-85°C.

Example 339

Isopropyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Melting point 158.3-159.8°C.

Example 340

n-Octyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Melting point 138-139.4°C.

Example 341

Preparation of 4-trifluoromethylbenzyl 4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

To the solution of tert-butyl 4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 319 (400 mg, 1.13 mmol) in methylene chloride (2 ml), trifluoroacetic acid (1 ml) was added followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in DMF (1 ml) and neutralized with triethylamine (1 ml).

To the solution, a mixture of 4-trifluoromethylbenzyl alcohol (297 mg, 1.69 mmol), 1,1'-carbonyldiimidazole (274 mg, 1.69 mmol) and DMF (1

ml) stirred at room temperature for 1 hour was added followed by stirring at room temperature for 3 hours. The reaction mixture was diluted with water and extracted with ethyl acetate twice. The organic phases were combined, washed with water twice and then with a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford 4-trifluoromethylbenzyl 4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (322 mg, yield 63%) as a light yellow powder.

Melting point 120-122°C.

Using corresponding starting materials gave compounds of Examples 342 and 343 in the same manner as in Example 341.

Example 342

4-Trifluoromethylbenzyl 4-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]piperazine-1-carboxylate

Light yellow powder, yield 68%, melting point 139-140°C.

Example 343

4-Trifluoromethylbenzyl 4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl]piperazine-1-carboxylate

Light yellow powder, yield 57%, melting point 130-133°C.

Example 344

Preparation of 3-(4-trifluoromethylphenyl)-2-propynyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate maleate

A mixture of 2-(4-tert-butoxycarbonyl-piperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 306 (220 mg, 0.6 mmol), trifluoroacetic acid (1 ml) and methylene chloride (2 ml) was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene (2 ml) chloride and neutralized with triethylamine (1 ml, 7.17 mmol). The resulting solution was concentrated under reduced pressure, and the residue was dissolved in DMF (2 ml).

To the solution, a mixture of 3-(4-trifluoromethylphenyl)-2-propyn-1-ol (110 ml, 0.55 mmol), 1,1'-carbonyldiimidazole (90 mg, 0.55 mmol) and DMF (2 ml) stirred at room temperature for 2 hours was added followed by stirring at room temperature overnight. The reaction mixture was diluted with water and extracted with ethyl acetate twice. The organic phases were combined, washed with water twice and then with a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 5/1).

The resulting free form was dissolved in

ethanol (5 ml) and added a solution of maleic acid (96 mg, 0.83 mmol) in ethanol (5 ml). The precipitates were filtered off to afford 3-(4-trifluoromethylphenyl)-2-propynyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate maleate (227 mg, yield 68%) as a white powder.

Melting point 166°C (decomposition).

Example 345

Preparation of 4-methylsulfanylbenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazine-1-carboxylate

A mixture of 2-(4-tert-butoxycarbonyl-piperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 306 (900 mg, 2.4 mmol) and trifluoroacetic acid (20 ml) was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene (20 ml) chloride and neutralized with triethylamine (6 ml, 43.05 mmol). The resulting mixture was concentrated under reduced pressure, and the residue was dissolved in DMF (5 ml).

To the solution, a mixture of 4-methylsulfanylbenzyl alcohol (470 mg, 3 mmol), 1,1'-carbonyldiimidazole (500 mg, 3.1 mmol) and DMF (10 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature overnight. To the reaction mixture, water was added, and the mixture

was extracted with ethyl acetate twice. The organic phases were combined, washed with water twice, and then with a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford 4-methylsulfanylbenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (860 mg, yield 79%) as a white powder. Melting point 118-120°C.

Example 346

Preparation of 4-methanesulfinylbenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazine-1-carboxylate

To a mixture of 4-methylsulfanylbenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 345 (300 mg, 0.67 mmol) and methylene chloride (10 ml), m-chloroperbenzoic acid (210 mg, 0.85 mmol) was added followed by stirring for 2 hours with cooling on ice-bath. The reaction mixture was washed with a saturated sodium sulfite solution, a saturated sodium hydrogencarbonate solution, and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from isopropyl alcohol-ether to afford 4-

methanesulfinylbenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (203 mg, yield 65%) as a white powder. Melting point 117-121°C.

Example 347

Preparation of 4-hydroxybenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

To a mixture of 4-(tert-butyldimethylsilanyloxy)benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (400 mg, 0.75 mmol) and THF(10 ml), a 1M solution of tetrabutylammonium fluoride in THF (0.8 ml, 0.8 mmol) was added followed by stirring for 20 minutes with cooling on ice-bath. To the reaction mixture, ethyl acetate was added, and the solution was washed with a saturated ammonium chloride solution, water and a saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure. To the residue, diethyl ether was added, and the precipitates were filtered off to afford 4-hydroxybenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (95 mg, yield 30%) as a light yellow powder.

^{1}H-NMR ($CDCl_3$) δppm:

1.59 (3H, s), 2.30 - 2.70 (4H, m), 2.56 (1H, d, J = 15.0 Hz), 2.86 (1H, d, J = 15.0 Hz), 3.10 - 3.55 (4H,

m), 3.91 (1H, d, J = 10.0 Hz), 4.28 (1H, d, J = 10.0 Hz), 5.03 (2H, s), 5.30 (1H, brs), 6.84 (2H, d, J = 8.0 Hz), 7.24 (2H, d, J = 8.0 Hz), 7.53 (1H, s).

Example 348

Preparation of 4-acetylbenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

A mixture of 4-(1,1-dimethoxyethyl)benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (600 mg, 1.23 mmol), 1 N hydrochloric acid (10 ml, 10 mmol) and THF (15 ml) was stirred at room temperature for 2 hours, then neutralized with a saturated sodium hydrogencarbonate solution, and the resulting mixture was extracted with ethyl acetate. The oranic phase was washed with water and then with a saturated saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure. To the residue, diethyl ether was added, and the precipitates were filtered off to afford 4-acetylbenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (558 mg, yield 99%) as a white powder.

Melting point 101-102°C.

Example 349

Preparation of 4-benzoylbenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Using 4-[dimethoxy(phenyl)methyl]benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (800 mg, 1.45 mmol) gave 4-benzoylbenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (630 mg, yield 86%) as a white powder in the same manner as in Example 348.

Melting point 105-107°C.

Example 350

Preparation of 4-aminobenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

A mixture of 4-(tert-butoxycarbonylamino)-benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (340 mg, 0.66 mmol), trifluoroacetic acid (2 ml) and methylene chloride (10 ml) was stirred at room temperature for 2 hours, and then neutralized with a saturated sodium hydrogencarbonate solution. The organic phase was washed with water and a saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure. To the residue, diethyl ether was added, and the precipitates were filtered off to afford 4-aminobenzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (100 mg, yield 37%) as a light yellow powder.

^{1}H-NMR ($CDCl_3$) δppm:

1.61 (3H, s), 2.35 - 2.70 (4H, m), 2.56 (1H, d, J = 15.0 Hz), 2.85 (1H, d, J = 15.0 Hz), 3.05 - 3.55 (4H, m), 3.69 (2H, brs), 3.91 (1H, d, J = 10.0 Hz), 4.28 (1H, d, J = 10.0 Hz), 4.98 (2H, s), 6.55 (2H, d, J = 8.0 Hz), 7.14 (2H, d, J = 8.0 Hz), 7.53 (1H, s).

Example 351

Preparation of 4-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid phenylamide hydrochloride

A mixture of 2-(4-tert-butoxycarbonyl-piperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 306 (130 mg, 0.35 mmol) and trifluoroacetic acid (3 ml) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride (3 ml), then neutralized with triethylamine (2 ml, 14.35 mmol). To the solution, phenylisocyanate (63 mg, 0.53 mmol) was added followed by stirring at room temperature for 30 minutes, and then diluted with water. The solution was extracted with methylene chloride, and the organic phase was dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford an amorphous form.

The amorphous form was dissolved in ethyl acetate. To the solution, a saturated hydrochloric

acid solution in ethyl acetate was added, and the resulting precipitates were filtered off to afford 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid phenylamide hydrochloride (124 mg, yield 55%) as a light yellow powder.

^{1}H-NMR (DMSO-d_6) δppm:

1.55 (3H, s), 2.50 - 2.56 (4H, m), 2.75 (2H, s), 3.21 - 3.40 (4H, m), 4.05 (1H, d, J = 10.7 Hz), 4.24 (1H, d, J = 10.7 Hz), 6.92 - 6.99 (1H, m), 7.21 - 7.28 (2H, m), 7.44 - 7.48 (2H, m), 8.13 (1H, s), 8.59 (1H, s).

Example 352

Preparation of 4-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid isopropylamide

A mixture of tert-butyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 306 (140 mg, 0.38 mmol) and trifluoroacetic acid (3 ml) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride (3 ml), then neutralized with triethylamine (2 ml, 14.35 mmol). To the solution, isopropylisocyanate (75 μl, 0.76 mmol) was added followed by stirring at room temperature for 1 hour, then diluted with water. The solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered.

The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid isopropylamide (90 mg, yield 67%) as a white powder.

Melting point 175-176.3°C.

Using corresponding starting materials gave compounds of Examples 353 and 354 in the same manner as in Example 352.

Example 353

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (3-chlorophenyl)-amide

^{1}H-NMR (DMSO-d_6) δppm:

1.56 (3H, s), 2.50 - 2.56 (4H, m), 2.77 (2H, s), 3.21 - 3.40 (4H, m), 4.08 (1H, d, J = 10.7 Hz), 4.26 (1H, d, J = 10.7 Hz), 6.95 (1H, bd, J = 8.0 Hz), 7.23 (1H, t, J = 8.0 Hz), 7.36 (1H, bd, J = 8.0 Hz), 7.61 (1H, t, J = 2.0 Hz), 8.13 (1H, s), 8.61 (1H, s).

Example 354

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid cyclohexylamide

Melting point 216.5-218.5°C.

Example 355

Preparation of 4-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)piperazine-1-carbothioic acid (4-chlorophenyl)amide

2-Methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 322 (196 mg, 0.73 mmol) was suspended in methylene chloride (10 ml), then neutralized with triethylamine (0.27 ml, 1.94 mmol). To the solution, 4-chlorophenyl isothiocyanate (140 mg, 0.83 mmol) was added followed by stirring at room temperature for 1 hour. The reaction mixture was washed with water, a saturated sodium hydrogencarbonate solution and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 30/1) to afford 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carbothioic acid (4-chlorophenyl)amide (128 mg, yield 40%) as a light brown powder.

Melting point 204-206°C (decomposition).

Using corresponding starting materials gave compounds of Examples 356 and 357 in the same manner as in Example 355.

Example 356

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carbothioic acid phenylamide

Melting point 164-165°C (decomposition).

Example 357

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

ylmethyl)piperazine-1-carbothioic acid (4-methoxyphenyl)amide

Melting point 189-191°C (decomposition).

Example 358

Preparation of 2-[4-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]benzoxazole

2-(4-tert-Butoxycarbonylpiperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 306 (500 mg, 1.36 mmol) was dissolved in trifluoroacetic acid (10 ml) followed by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, and added methylene chloride (1 ml) and triethylamine (1 ml). The solution was stirred at room temperature for 5 minutes, and then concentrated under reduced pressure. The residue was dissolved in methylene chloride. To the solution, 2-chloro-benzoxazole (0.19 ml, 1.63 mmol) and triethylamine (0.23 ml, 1.63 mmol) were added followed by stirring at room temperature for 1 hour. The reaction mixture was poured into water, and extracted with methylene chloride. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from

methylene chloride-diisopropyl ether to afford 2-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]benzoxazole (325 mg, yield 62%) as a white powder.

MS 384(M^+)

Melting point 228.0-229.5°C.

Using corresponding starting materials gave compounds of Examples 359 to 361 in the same manner as in Example 358.

Example 359

2-[4-(6-Nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]benzoxazole

White powder, yield 74%

MS 370(M^+)

Melting point 206-209°C (decomposition).

Example 360

2-{4-[2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]piperazin-1-yl}benzoxazole

White powder, yield 73%

MS 398(M^+)

Melting point 187.6-189.6°C.

Example 361

2-{4-[3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl]piperazin-1-yl}benzoxazole

White powder, yield 90%

MS 412(M^+)

Melting point 172.0-174.4°C.

Example 362

Preparation of tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-carboxylate

(R)-2-Chloro-1-[2-hydroxy-3-(4-methylbenzenesulfonyloxy)propyl]-4-nitroimidazole prepared in Example 8 (16.86 g, 44.86 mmol) and tert-butyl piperazine-1-carboxylate (8.36 g, 44.89 mmol) were dissolved in acetonitrile (100 ml). To the solution, triethylamine (6.3 ml, 45.2 mmol) was added followed by stirring under reflux for 6 hours. The reaction mixture was allowed to return to room temperature, and concentrated under reduced pressure. To the residue, water (100 ml) was added and extracted with ethyl acetate (100 ml) twice. The organic phases were combined, washed with water (100 ml) and a saturated saline solution (100 ml) in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 40/1) and then recrystallized from ethyl acetate/n-hexane to afford tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-carboxylate (11.61 g, yield 66%) as a light yellow powder.

^{1}H-NMR ($CDCl_3$) δppm:

1.46 (9H, s), 2.21 - 2.50 (4H, m), 2.54 - 2.70 (2H, m), 3.39 - 3.48 (4H, m), 3.65 (1H, s), 3.89 - 4.10 (2H, m), 4.20 (1H, dd, J = 1.9 Hz, 13.5 Hz), 8.00 (1H, s).

Example 363

Preparation of tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-carboxylate (alternative synthesis of the compound of Example 362)

A mixture of (R)-2-chloro-1-(oxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 9 (1 g, 4.91 mmol), tert-butyl piperazine-1-carboxylate (1.01 g, 5.40 mmol) and DMF (3 ml) was stirred at 70°C for 6 hours. The reaction mixture was allowed to return to room temperature and added water (7 ml). The precipitates were filtered off, and purified by silica gel column chromatography (methylene chloride/methanol = 40/1) to afford tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-carboxylate (967 mg, 51%) as a light yellow powder.

Example 364

Preparation of tert-butyl (R)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-carboxylate

A mixture of 2-chloro-4-nitro-1H-imidazole (6.1 g, 41.35 mmol), (S)-(+)-glycidyl tosylate (12.27 g, 53.75 mmol) and sodium hydrogencarbonate (7.3 g, 86.89 mmol) in ethanol (30 ml) was stirred under reflux for 9 hours. The reaction mixture was allowed to return to room temperature, then diluted with water, and the solution was extracted with methylene chloride twice. The extract was washed with a saturated saline

solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated to afford a foam. The resulting foam was dissolved in DMF (60 ml). To the solution, tert-butyl piperazine-1-carboxylate (8.47 g, 45.48 mmol), triethylamine (6.92 ml, 49.64 mmol) and sodium iodide (6.82 g, 45.5 mmol) were added followed by stirring at room temperature for 24 hours. The reaction mixture was poured into water, and extracted with ethyl acetate twice. The organic phases were combined, washed with water three times, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate) to afford tert-butyl (R)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazin-1-carboxylate (6.43 g, yield 40%) as a light yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.48 (9H, s), 2.16 - 2.50 (4H, m), 2.55 - 2.69 (2H, m), 3.37 - 3.50 (4H, m), 3.65 (1H, s), 3.90 - 4.25 (3H, m), 8.00 (1H, s).

Example 365

Preparation of tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate

A mixture of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (7.00 g, 32.2 mmol) and tert-butyl piperazine-1-

carboxylate (6.29 g, 33.8 mmol) and DMF (70 ml) was stirred at 70°C for 8 hours. The reaction mixture was allowed to return to room temperature, then diluted with water, and then the solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water three times, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. To the residue, diethyl ether was added. The precipitates were filtered off, and dried at room temperature under reduced pressure to afford tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-carboxylate (10.25 g, yield 79%) as a light yellow powder.

Optical purity >98.4% e.e.

$[\alpha]_D^{27}$ = 25.488 (concentration: 1.024, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.14 (3H, s), 1.46 (9H, s), 2.34 (1H, d, J = 13.9 Hz), 2.47 - 2.67 (5H, m), 3.26 (1H, s), 3.44 (4H, t, J = 4.4 Hz), 3.99 (2H, s), 8.04 (1H, s).

Example 366

Preparation of tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate (alternative synthesis of the compound of Example 365)

To the solution of 2-Chloro-4-nitro-1H-imidazole (89.4 g, 606 mmol) and tert-butyl (S)-4-(2-methyloxiran-2-ylmethyl)piperazine-1-carboxylate (119

g, 466 mmol) in ethanol (475 ml), sodium hydrogencarbonate (58.7 g, 699 mmol) was added followed by stirring under reflux for 6 hours. The reaction mixture was concentrated under reduced pressure, and the residue was added water. The mixture was extracted with ethyl acetate, and the extract was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was dispersed into ethyl acetate, and filtered off to afford a solid. The filtrate was concentrated, and the residue was purified by silica gel column chromatography (n-hexane/acetone = 3/1) to afford a solid. The solids were combined and dried under reduced pressure to afford tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate (84.7 g, yield 45%) as a white powder.

Example 367

Preparation of (R)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate

A mixture of (S)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 18 (440 mg, 2.02 mmol), tert-butyl piperazine-1-carboxylate (414 mg, 2.22 mmol) and DMF (4 ml) was stirred at 55-60°C for 9 hours. The reaction mixture was allowed to return to room temperature, then diluted with water (24 ml), and the solution was extracted with ethyl acetate (10 ml) twice. The organic phases were

combined, washed with water (20 ml) three times and a saturated saline solution (10 ml), dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue treated with diethyl ether to afford tert-butyl (R)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate (662 mg, yield 81%) as a light yellow powder.

^{1}H-NMR ($CDCl_3$) δppm:

1.15 (3H, s), 1.45 (9H, s), 2.34 (1H, d, J = 13.9 Hz), 2.48 - 2.67 (5H, m), 3.27 (1H, s), 3.44 (4H, t, J = 4.4 Hz), 3.99 (2H, s), 8.04 (1H, s).

Using 2-chloro-4-nitro-1H-imidazole and tert-butyl (R)-4-(2-methyloxiran-2-ylmethyl)piperazine-1-carboxylate gave the compound of Example 368 in the same manner as in Example 366.

Example 368

Tert-butyl (R)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate (alternative synthesis of the compound of Example 367) White powder, yield 20%.

Example 369

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]propan-2-ol

To a suspension of (S)-1-(2-methyloxiran-2-ylmethyl)-4-(4-trifluoromethoxyphenyl)piperazine (0.43 g, 1.37 mmol) and 2-chloro-4-nitro-1H-imidazole (0.22

g, 1.51 mmol) in acetonitrile (4 ml), sodium hydrogencarbonate (0.17 g, 2.06 mmol) was added followed by stirring under reflux for 9 hours. To the reaction mixture, water was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 3/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]propan-2-ol (0.20 g, yield 31%) as a light yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.18 (3H, s), 2.41 (1H, d, J = 13.8 Hz), 2.56 (1H, d, J = 13.8 Hz), 2.67 - 2.80 (2H, m), 2.85 - 2.96 (2H, m), 3.13 - 3.25 (4H, m), 4.03 (2H, s), 6.83 - 6.93 (2H, m), 7.07 - 7.17 (2H, m), 8.07 (1H, s).

Example 370

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-chlorophenyl)piperazin-1-yl]propan-2-ol

(R)-2-Chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (20 g, 91.9 mmol) and 1-(4-chlorophenyl)piperazine (20.8 g, 0.11 mol) were added to DMF (200 ml) followed by stirring at 70-75°C for 5 hours. The reaction mixture was allowed to return to room temperature, poured into water, and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over

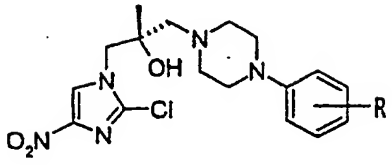
sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 20/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-chlorophenyl)piperazin-1-yl]propan-2-ol (33.0 g, yield 87%) as a yellow amorphous form.

^{1}H-NMR ($CDCl_3$) δppm:

1.53 (3H, s), 2.42 (1H, d, J = 13.9 Hz), 2.55 (1H, d, J = 13.9 Hz), 2.67 - 2.76 (2H, m), 2.81 - 2.90 (2H, m), 3.13 - 3.17 (4H, m), 3.43 (1H, s), 4.03 (2H, s), 6.78 - 6.85 (2H, m), 7.16 - 7.23 (2H, m), 8.06 (1H, s).

Using corresponding starting materials gave compounds of Examples 371 to 384 shown in the following table in the same manner as in Example 370.

Table 17



Example	R	Yield (%)	^{1}H NMR ($CDCl_3$) δ
371	4-CF_3	82	1.18(3H, s), 2.41(1H, d, J=13.9Hz), 2.56(1H, d, J=13.9Hz), 2.68-2.79(2H, m), 2.82-2.91(2H, m), 3.26-3.31(5H, m), 4.03(2H, s), 6.91(2H, d, J=8.7Hz), 7.49(2H, d, J=8.7Hz), 8.06(1H, s).
372	4-H	92	1.17(3H, s), 2.40(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.69-2.78(2H, m), 2.83-2.91(2H, m), 3.18-3.22(4H, m), 3.42(1H, s), 4.01(2H, s), 6.85-6.93(3H, m), 7.24-7.31(2H, m), 8.06(1H, s).
373	4-F	43	1.16(3H, s), 2.41(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.69-2.77(2H, m), 2.82-2.91(2H, m), 3.10-3.14(4H, m), 3.41(1H, s), 4.01(2H, s), 6.83-7.00(4H, m), 8.06(1H, s).
374	4-OMe	99	1.15(3H, s), 2.42(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.69-2.78(2H, m), 2.82-2.91(2H, m), 3.07-3.11(4H, m), 3.77(3H, s), 4.02(2H, s), 6.81-6.91(4H, m), 8.07(1H, s).
375	4-COOEt	100	1.17(3H, s), 1.37(3H, t, J=7.1Hz), 2.42(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.68-2.76(2H, m), 2.81-2.89(2H, m), 3.31-3.35(4H, m), 3.40(1H, s), 4.04(2H, s), 4.33(2H, q, J=7.1Hz), 6.83-6.87(2H, m), 7.90-7.95(2H, m), 8.06(1H, s).
376	4-Me	86	1.15(3H, s), 2.27(3H, s), 2.41(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.68-2.77(2H, m), 2.82-2.90 (2H, m), 3.12-3.16(4H, m), 3.47(1H, s), 4.01(2H, s), 6.81-6.85(2H, m), 7.06-7.09(2H, m), 8.06(1H, s).
377	4-CN	99	1.18(3H, s), 2.43(1H, d, J=13.9Hz), 2.56(1H, d, J=13.9Hz), 2.66-2.75(2H, m), 2.81-2.90(2H, m), 3.31-3.35(4H, m), 3.51(1H, s), 4.03(1H, d, J=14.3Hz), 4.09(1H, d, J=14.3Hz), 6.82-6.88(2H, m), 7.46-7.52(2H, m), 8.07(1H, s).
378	3,4-di-Cl	99	1.17(3H, s), 2.41(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.68-2.76(2H, m), 2.80-2.89(2H, m), 3.15-3.19(4H, m), 3.40(1H, s), 4.03(2H, s), 6.72(1H, dd, J=8.9, 2.9Hz), 6.94(1H, d, J=2.9Hz), 7.28(1H, d, J=8.9Hz), 8.05(1H, s).
379	3-CF_3	99	1.17(3H, s), 2.42(1H, d, J=13.9Hz), 2.56(1H, d, J=13.9Hz), 2.69-2.78(2H, m), 2.83-2.93(2H, m), 3.22-3.27(4H, m), 3.36(1H, s), 4.03(2H, s), 7.03-7.11(3H, m), 7.32-7.39(1H, m), 8.06(1H, s).

Table 17 (Contn'd)

380	2-CF_3	99	1.16(3H, s), 2.44(1H, d, J=14.0Hz), 2.57(1H, d, J=14.0Hz), 2.67-2.78(2H, m), 2.81-2.91(2H, m), 2.93-2.96(4H, m), 3.81(1H, s), 4.05(2H, s), 7.21-7.27(1H, m), 7.35-7.39(1H, m), 7.50-7.57(1H, m), 7.60-7.64(1H, m), 8.11(1H, s).
381	4-Cl-3-CF_3	99	1.18(3H, s), 2.42(1H, d, J=13.9Hz), 2.56(1H, d, J=13.9Hz), 2.68-2.77(2H, m), 2.83-2.92(2H, m), 3.19-3.24(4H, m), 3.40(1H, s), 4.04(2H, s), 6.95(1H, dd, J=8.9, 2.9Hz). 7.16(1H, d, J=2.9Hz), 7.34(1H, d, J=8.9Hz), 8.06(1H, s).
382	4-COO^{t}Bu	99	1.17(3H, s), 1.57(9H, s), 2.42(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.67-2.76(2H, m), 2.81-2.90(2H, m), 3.29-3.33(4H, m), 3.51(1H, s), 4.04(2H, s), 6.84(2H, d, J=9.0Hz), 7.87(2H, d, J=9.0Hz), 8.07(1H, s).
383	2-F	99	1.16(3H, s), 2.42(1H, d, J=13.9Hz), 2.57(1H, d, J=13.9Hz), 2.71-2.80(2H, m), 2.85-2.96(2H, m), 3.10-3.14(4H, m), 3.56(1H, s), 4.02(2H, s), 6.91-7.10(4H, m), 8.07(1H, s).
384	4-NMe_2	82	1.14(3H, s), 2.40(1H, d, J=13.9Hz), 2.54(1H, d, J=13.9Hz), 2.70-2.77(2H, m), 2.81-2.91(8H, m), 3.05-3.09(4H, m), 3.66(1H, s), 4.01(2H, s), 6.72-6.76(2H, m), 6.86-6.91(2H, m), 8.07(1H, s).

Using corresponding starting materials gave compounds of Examples 385 and 386 in the same manner as in Example 370.

Example 385

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-pyridyl)piperazin-1-yl]propan-2-ol

Yield 100%

^{1}H-NMR ($CDCl_3$) δppm:

1.18 (3H, s), 2.44 (1H, d, J = 13.9 Hz), 2.56 (1H, d, J = 13.9 Hz), 2.63 - 2.73 (2H, m), 2.77 - 2.91 (2H, m), 3.31 - 3.35 (4H, m), 3.54 (1H, s), 4.03 - 4.12 (2H, m), 6.63 - 6.66 (2H, m), 8.09 (1H, s), 8.23 - 8.27 (2H, m).

Example 386

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(3-

pyridyl)piperazin-1-yl]propan-2-ol

Yield 81%

^{1}H-NMR ($CDCl_3$) δppm:

1.17 (3H, s), 2.44 (1H, d, J = 13.9 Hz), 2.57 (1H, d, J = 13.9 Hz), 2.67 - 2.79 (2H, m), 2.84 - 2.93 (2H, m), 3.20 - 3.25 (4H, m), 3.85 (1H, bs), 4.06 (2H, s), 7.16 - 7.19 (2H, m), 8.07 - 8.11 (2H, m), 8.26 - 8.28 (1H, m).

Using (R)-2-chloro-4-nitro-1-(oxiran-2-ylmethyl)imidazole prepared in Example 9 gave compounds of Examples 387 to 389 in the same manner as in Example 370.

Example 387

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-[4-(4-fluorophenyl)piperazin-1-yl]propan-2-ol

Yield 86%

^{1}H-NMR ($CDCl_3$) δppm:

2.27 - 2.36 (1H, m), 2.49 - 2.63 (3H, m), 2.78 - 2.88 (2H, m), 2.97 - 3.18 (4H, m), 3.74 (1H, br), 3.96 - 4.08 (2H, m), 4.18 - 4.24 (1H, m), 6.84 - 7.01 (4H, m), 8.02 (1H, s).

Example 388

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-[4-(4-trifluoromethylphenyl)piperazin-1-yl]propan-2-ol

Yield 49%

^{1}H-NMR ($CDCl_3$) δppm:

2.27 - 2.36 (1H, m), 2.49 - 2.63 (3H, m), 2.78 - 2.87 (2H, m), 3.28 - 3.31 (4H, m), 3.62 (1H, br), 3.95 -

4.11 (2H, m), 4.19 - 4.25 (1H, m), 6.92 (2H, d, J = 8.6 Hz), 7.49 (2H, d, J = 8.6 Hz), 8.02 (1H, s).

Example 389

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-3-[4-(4-cyanophenyl)piperazin-1-yl]propan-2-ol

Yield 100%

^{1}H-NMR ($CDCl_3$) δppm:

2.28 - 2.37 (1H, m), 2.49 - 2.63 (3H, m), 2.76 - 2.85 (2H, m), 3.28 - 3.36 (4H, m), 3.58 (1H, br), 3.96 - 4.12 (2H, m), 4.19 - 4.25 (1H, m), 6.87 (2H, d, J = 8.9 Hz), 7.51 (2H, d, J = 8.9 Hz), 8.01 (1H, s).

Example 390

Preparation of 4-trifluoromethoxybenzyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate

A mixture of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (15 g, 68.93 mmol) and 4-trifluoromethoxybenzyl piperazine-1-carboxylate (25.17 g, 82.72 mmol) in DMF (75 ml) was stirred at 65-70°C for 20 hours. The reaction mixture was allowed to return to room temperature and poured into water (475 ml), and extracted with ethyl acetate (150 ml). The aqueous layer was extracted with ethyl acetate (150 ml) again. The organic phases were combined, washed with water (400 ml) 3 times and a saturated saline solution (100 ml), dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to afford 4-trifluoromethoxybenzyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate (29.98 g, yield 83%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.15 (3H, s), 2.36 (1H, d, J = 14.0 Hz), 2.42 - 2.75 (5H, m), 3.18 (1H, s), 3.42 - 3.58 (4H, m), 4.00 (2H, s), 5.12 (2H, s), 7.21 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 8.6 Hz), 8.03 (1H, s).

Example 391

Preparation of 3-(4-trifluoromethylphenyl)-2-propenyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate

A mixture of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (4.24 g, 19.48 mmol) and 3-(4-trifluoromethylphenyl)-2-propenyl piperazine-1-carboxylate (6.73 g, 21.41 mmol) in DMF (21 ml) were stirred at 50-55°C for 24 hours. The reaction mixture was allowed to return to room temperature and poured into water (90 ml), and extracted with ethyl acetate (60 ml). The aqueous layer was extracted with ethyl acetate (60 ml) again. The organic phases were combined, washed with water (90 ml) 3 times and a saturated saline solution (60 ml), dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and

the residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to afford 3-(4-trifluoromethylphenyl)-2-propenyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate (9.29 g, yield 90%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.16 (3H, s), 2.36 (1H, d, J = 14.0 Hz), 2.43 - 2.76 (5H, m), 3.17 (1H, s), 3.48 - 3.67 (4H, m), 4.00 (2H, s), 4.78 (2H, dd, J = 1.0 Hz, 6.1 Hz), 6.33 - 6.48 (1H, m), 6.66 (1H, d, J = 15.9 Hz), 7.48 (2H, d, J = 8.3 Hz), 7.58 (2H, d, J = 8.3 Hz), 8.04 (1H, s).

Using corresponding starting materials gave the compound of Example 392 in the same manner as in Example 391.

Example 392

3-(4-Trifluoromethoxyphenyl)-2-propenyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate

^{1}H-NMR ($CDCl_3$) δppm:

1.15 (3H, s), 2.36 (1H, d, J = 13.9 Hz), 2.51 (1H, d, J = 13.9 Hz), 2.48 - 2.63 (2H, m), 2.63 - 2.78 (2H, m), 3.17 (1H, s), 3.39 - 3.63 (4H, m), 4.00 (2H, s), 4.75 (2H, dd, J = 1.1 Hz, 6.3 Hz), 6.28 (1H, dt, J = 6.3 Hz, 15.9 Hz), 6.62 (1H, d, J = 15.9 Hz), 7.15 - 7.18 (2H, m), 7.38 - 7.42 (2H, m), 8.03 (1H, s).

Example 393

Preparation of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate prepared in Example 365 (10.25 g, 25.4 mmol) was dissolved in DMF (30 ml). To the solution, sodium hydride (1.12 g, 27.9 mmol) was added followed by stirring for 2 hours with cooling on ice-bath. To the reaction mixture, ethyl acetate (10 ml) and water (70 ml) were added. The precipitates were filtered off, and washed with water. The crude solids were recrystallized from ethyl acetate (70 ml) to afford tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (6.62 g, yield 71%) as a light yellow powder.

Optical purity >99.5% e.e.

$[\alpha]_D^{27}$ = -20.953° (concentration: 0.492, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.44 (9H, s), 1.62 (3H, s), 2.45 - 2.66 (5H, m), 2.87 (1H, d, J = 14.9 Hz), 3.29 (4H, br), 3.92 (1H, d, J = 9.7 Hz), 4.30 (1H, d, J = 9.7 Hz), 7.53 (1H, s).

Example 394

Preparation of tert-butyl (S)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Using tert-butyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-

carboxylate prepared in Example 363 (11 g, 28.22 mmol) gave tert-butyl (S)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (7.5 g, yield 75%) as a light yellow powder in the same manner as in Example 393.

Optical purity 96.6% e.e.

$[\alpha]_D^{22}$ = -11.91° (concentration: 1.016, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.45 (9H, s), 2.49 - 2.59 (4H, m), 2.85 (2H, d, J = 5.2 Hz), 3.33 - 3.44 (4H, m), 4.19 (1H, dd, J = 6.9 Hz, 10.2 Hz), 4.35 (1H, dd, J = 6.9 Hz, 10.2 Hz), 5.36 - 5.49 (1H, m), 7.55 (1H, s).

Example 395

Preparation of tert-butyl (R)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Tert-butyl (R)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxypropyl]piperazine-1-carboxylate prepared in Example 364 (6.43 g, 16.49 mmol) was dissolved in 1,4-dioxane (35 ml). To the solution, sodium hydride (730 mg, 18.25 mmol) was added with cooling on ice-bath, and the resulting solution was stirred at room temperature overnight and then stirred under reflux for 24 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added slowly, the mixture was extracted with methylene chloride twice, dried over sodium sulfate and

then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) to afford tert-butyl (R)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (1.23 g, yield 21%) as a white powder.

Optical purity >99% e.e.

$[\alpha]_D^{27}$ = 11.635° (concentration: 1.004, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.45 (9H, s), 2.50 - 2.61 (4H, m), 2.85 (2H, d, .J = 5.3 Hz), 3.31 - 3.50 (4H, m), 4.18 (1H, dd, J = 6.9 Hz, 10.2 Hz), 4.35 (1H, dd, J = 8.4 Hz, 10.2 Hz), 5.35 - 5.50 (1H, m), 7.55 (1H, s).

Example 396

Preparation of tert-butyl (R)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Tert-butyl (R)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate prepared in Example 368 (376 mg, 0.93 mmol) was dissolved in 1,4-dioxane (10 ml). To the solution, sodium hydride (45 mg, 1.12 mmol) was added with cooling on ice-bath, and the resulting solution was stirred at room temperature for 30 minutes and then stirred under reflux for 24 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added slowly, and the

solution was extracted with ethyl acetate twice. The organic phase was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/acetone = 3/1) to afford tert-butyl (R)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-carboxylate (239 mg, yield 70%) as a white powder. Optical purity 99.2% e.e.

$[\alpha]_D^{27}$ = 21.073° (concentration: 0.522, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.45 (9H, s), 1.61 (3H, s), 2.45 - 2.64 (5H, m), 2.87 (1H, d, J = 14.9 Hz), 3.29 (4H, br), 3.92 (1H, d, J = 9.7 Hz), 4.33 (1H, d, J = 9.7 Hz), 7.52 (1H, s).

Example 397

Preparation of (S)-2-[4-(4-trifluoromethoxyphenyl)-piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

To a solution of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethoxy-phenyl)piperazin-1-yl]propan-2-ol prepared in Example 369 (5.85 g, 12.61 mmol) in THF (150 ml), sodium hydride (0.66 g, 18.92 mmol) was added with cooling on ice-bath followed by stirring under reflux for 6 hours. The reaction mixture was concentrated under reduced pressure, and the residue was added water and ethyl acetate. The precipitates were filtered off, purified by silica gel column chromatography (n-hexane/ethyl

acetate = 1/1) and recrystallized from isopropanol to afford (S)-2-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (2.58 g, yield 48%) as a light yellow solid. Optical purity 99.8% e.e.

$[\alpha]_D^{26}$ = 8.80° (concentration: 1.000, $CHCl_3$)

Melting point 129-130°C.

Example 398

Preparation of (S)-2-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-chlorophenyl)piperazin-1-yl]propan-2-ol prepared in Example 370 (33.0 g, 79.7 mmol) was dissolved in DMF (300 ml). To the solution, sodium hydride (3.7 g, 91.6 mmol) was added with cooling on ice-bath followed by stirring at room temperature overnight. To the reaction mixture, ice-water and ethyl acetate were added, and the solution was vigorously stirred. The precipitates were filtered off, washed with water and ethyl acetate, and dried under reduced pressure to afford 23.2 g of a crude light yellow powder. The crude powder was combined with another crude powder synthesized in the same manner (50 g), and the mixture was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 50/1) and crystallized from methylene chloride-ethyl acetate to afford (S)-2-[4-(4-

chlorophenyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (45 g, yield 90%) as a white powder.

Optical purity 99.6% e.e.

$[\alpha]_D^{22}$ = -10.20° (concentration: 0.5, $CHCl_3$)

Melting point 218-219.6°C.

Using corresponding starting materials gave compounds of Examples 399 to 403 in the same manner as in Example 398.

Example 399

(S)-2-[4-(4-Fluorophenyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 42%, $[\alpha]_D^{28}$ = 2.10° (concentration: 0.5, $CHCl_3$)

Melting point 178.5-179.5°C.

Example 400

(S)-2-[4-(3-Pyridyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 42%, melting point 145-147.7°C.

Example 401

(S)-2-[4-(4-Pyridyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 3%

^{1}H-NMR ($CDCl_3$) δppm:

1.65 (3H, s), 2.62 (1H, d, J = 14.8 Hz), 2.64 - 2.71 (2H, m), 2.79 - 2.89 (2H, m), 2.92 (1H, d, J = 14.8 Hz), 3.15 - 3.30 (4H, m), 3.95 (1H, d, J = 9.7 Hz), 4.33 (1H, d, J = 9.7 Hz), 6.60 (2H, d, J = 6.2 Hz), 7.53 (1H, s), 8.26 (2H, d, J = 6.2 Hz).

Example 402

(S)-2-[4-(4-Trifluoromethylphenyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 175.8-176.6°C.

Example 403

(S)-2-[4-(4-Cyanophenyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 211-211.5°C.

Example 404

Preparation of (S)-2-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

1-(4-Chlorophenyl)piperazine dihydrochloride (1.31 g, 4.86 mmol) was added to a sodium hydroxide solution, and the resulting mixture was extracted with methylene chloride. The extract was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure to afford 1-(4-chlorophenyl)piperazine.

Then, a mixture of 1-(4-chlorophenyl)-piperazine obtained, (R)-2-chloro-1-(oxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 9 (763 mg, 3.75 mmol) and DMF (5 ml) was stirred at 70°C for 6 hours. To the solution, sodium hydride (219 mg, 5.48 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 2 hours. To the reaction mixture, ice-water was added, and precipitates were filtered off. The resulting solids were recrystallized from acetone/water to afford (S)-2-[4-

(4-chlorophenyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (250 mg, yield 18%) as a light yellow powder.

Melting point 183-183.5°C.

Example 405

Preparation of 4-trifluoromethoxybenzyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

4-Trifluoromethoxybenzyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-piperazine-1-carboxylate prepared in Example 390 (4.3 g, 8.24 mmol) was dissolved in DMF (13 ml). To the solution, sodium hydride (430 mg, 10.7 mmol) was added followed by stirring at the same temperature for 2 hours with cooling on ice-bath. To the reaction mixture, ethyl acetate (4.3 ml) and water (30 ml) were added in this order, and the solution was stirred for 30 minutes. The precipitates were filtered off and washed with water. The solids obtained were recrystallized from ethyl acetate/isopropyl ether and then recrystallized from isopropyl alcohol to afford 4-trifluoromethoxybenzyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (3.15 g, yield 79%) as a white powder.

Melting point 139.5-140.5°C

Optical purity >99.5% e.e.

$[\alpha]_D^{27}$ = 18.04° (concentration: 1.020, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.60 (3H, s), 2.39 - 2.75 (5H, m), 2.87 (1H, d, J = 14.9 Hz), 3.14 - 3.56 (4H, m), 3.93 (1H, d, 9.7 Hz), 4.29 (1H, d, J = 9.7 Hz), 5.10 (2H, s), 7.19 (2H, d, J = 8.6 Hz), 7.36 (2H, d, J = 8.6 Hz), 7.54 (1H, s).

Example 406

Preparation of 3-(4-trifluoromethylphenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

3-(4-Trifluoromethylphenyl)-2-propenyl (S)-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate prepared in Example 391 (13.2 g, 24.81 mmol) was dissolved in DMF (40 ml). To the solution, sodium hydride (1.19 g, 29.78 mmol) was added followed by stirring for 1.5 hours with cooling on ice-bath. To the reaction mixture, ethyl acetate (13 ml) and water (92 ml) were added in this order followed by stirring for 30 minutes. The precipitates were filtered off, washed with water and purified by silica gel column chromatography (ethyl acetate) to afford 3-(4-trifluoromethylphenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (10.17 g, yield 83%) as a light yellow powder.

Melting point 132-133°C

Optical purity 99.0% e.e.

$[\alpha]_D^{27}$ = -21.73° (concentration: 0.866, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.62 (3H, s), 2.48 - 2.75 (5H, m), 2.88 (1H, d, J =

14.9 Hz), 3.15 - 3.57 (4H, m), 3.94 (1H, d, J = 9.7 Hz), 4.29 (1H, d, J = 9.7 Hz), 4.75 (2H, d, J = 1.15 Hz, 6.0 Hz), 6.29 - 6.42 (1H, m), 6.64 (1H, d, J = 15.9 Hz), 7.47 (2H, d, J = 8.4 Hz), 7.52 - 7.62 (3H, m).

Using corresponding starting materials gave the compound of Example 407 in the same manner as in Example 406.

Example 407

3-(4-Trifluoromethoxyphenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Melting point 91-93°C

$[\alpha]_D^{27}$ = -21.88° (concentration: 0.786, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.54 (3H, s), 2.38 - 2.71 (5H, m), 2.84 (1H, d, J = 14.9 Hz), 3.13 - 3.54 (4H, m), 3.92 (1H, d, J = 9.7 Hz), 4.29 (1H, d, J = 9.7 Hz), 4.73 (2H, dd, J = 1.2 Hz, 6.2 Hz), 6.15 - 6.33 (1H, m), 6.60 (1H, d, J = 16.0 Hz), 7.16 (2H, d, J = 8.7 Hz), 7.40 (2H, d, J = 8.7 Hz), 7.53 (1H, s).

Example 408

Preparation of (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride

Tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 393 (1.46 g, 3.98 mmol) was dissolved in trifluoroacetic acid (30 ml) followed

by stirring at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methanol (30 ml). To the solution, a solution of a saturated hydrogen chloride in ethyl acetate was added followed by stirring for 30 minutes with cooling on ice-bath. The precipitates were filtered off to afford (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydro-imidazo[2,1-b]oxazole dihydrochloride (994 mg, yield 73%) as a yellow powder.

^{1}H-NMR (DMSO-d_6) δppm:

1.63 (3H, s), 2.80 - 3.36 (6H, m), 4.11 (1H, d, J = 11.0 Hz), 4.25 - 4.98 (5H, m), 8.15 (1H, s), 9.31 (2H, br).

Example 409

Preparation of (S)-6-nitro-2-[4-(4-trifluoromethyl-benzyl)piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of tert-butyl (S)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 394 (100 mg, 0.27 mmol) and trifluoroacetic acid (2 ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (5 ml) and neutralized with triethylamine (1 ml, 7.17 mmol), and then the solution was concentrated under reduced pressure. The residue was dissolved in methanol (5 ml), and the

solution was added 4-trifluoromethylbenzaldehyde (148 mg, 0.85 mmol), sodium cyanotrihydroborate (53 mg, 0.85 mmol), and acetic acid (49 μl, 0.85 mmol) in this order followed by stirring at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure. To the residue, a saturated sodium hydrogencarbonate solution was added, and the solution was extracted with methylene chloride twice. The organic phases were combined, washed with a saturated sodium hydrogencarbonate solution and a saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 1/1) to afford (S)-6-nitro-2-[4-(4-trifluoromethylbenzyl)piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole (53 mg, yield 46%) as a light yellow powder.

Melting point 149-150°C.

Example 410

Preparation of (S)-2-[4-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of tert-butyl (S)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 394 (7.2 g, 20.26 mmol), trifluoroacetic acid (24 ml) and methylene chloride (72 ml) was stirred at room temperature for 2 hours. The reaction mixture was concentrated under

reduced pressure, and the residue was dissolved in methylene chloride (100 ml), then neutralized with triethylamine (20 ml, 143.49 mmol). The solution was concentrated under reduced pressure, and the residue was dissolved in methanol (72 ml). To the solution, 4-phenylbenzaldehyde (7.38 g, 40.52 mmol), sodium cyanotrihydroborate (3.82 g, 60.78 mmol), and acetic acid (3.48 ml, 60.78 mmol) were added in this order followed by stirring at room temperature for 24 hours. The precipitates were filtered off, washed with methanol, and purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to afford (S)-2-[4-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (5.52 g, yield 65%) as a yellow powder.

Optical purity >99.0% e.e.

$[\alpha]_D^{28}$ = -28.261° (concentration: 0.046, DMSO)

Melting point 207-208°C.

Example 411

Preparation of (R)-2-[4-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of tert-butyl (R)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 395 (101.5 mg, 0.29 mmol) and trifluoroacetic acid (2 ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (5 ml) and neutralized

with triethylamine (2 ml, 14.35 mmol), and then the solution was concentrated under reduced pressure. The residue was dissolved in methanol (5 ml). To the solution, 4-phenylbenzaldehyde (156 mg, 0.86 mmol), sodium cyanotrihydroborate (53 mg, 0.84 mmol) and acetic acid (0.05 ml, 0.87 mmol) were added in this order followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure. To the residue, a saturated sodium hydrogencarbonate solution was added, and the solution was extracted with methylene chloride twice. The organic phases were combined, washed with a saturated sodium hydrogencarbonate solution and a saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate) to afford (R)-2-[4-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (56 mg, yield 46%) as a white powder.

$[\alpha]_D^{28}$ = 28.261° (concentration: 0.046, DMSO).

Melting point 224-225°C

Using corresponding starting materials gave the compound of Example 412 in the same manner as in Example 411.

Example 412

(R)-6-Nitro-2-[4-(4-trifluoromethylbenzyl)piperazin-1-

ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

Yield 48%, melting point 141-143°C.

Example 413

Preparation of (S)-2-methyl-6-nitro-2-[4-(4'-trifluoromethylbiphenyl-4-ylmethyl)piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazine-1-carboxylate prepared in Example 393 (1.7 g, 4.6 mmol), trifluoroacetic acid (10 ml) and methylene chloride (30 ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methanol (30 ml). To the solution, 4'-trifluoromethylbiphenyl-4-carboaldehyde (2.3 g, 9.19 mmol), sodium cyanotrihydroborate (580 mg, 9.23 mmol) and acetic acid (0.55 ml, 9.62 mmol) were added in this order followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure. To the residue, a saturated sodium hydrogencarbonate solution was added, and the solution was extracted with methylene chloride twice. The organic phases were combined, washed with a saturated sodium hydrogencarbonate solution and a saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography

(methylene chloride/methanol = 50/1) to afford (S)-2-methyl-6-nitro-2-[4-(4'-trifluoromethylbiphenyl-4-ylmethyl)piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole (1.47 g, yield 63%) as a white powder.

$[\alpha]_D^{28}$ = 1.831° (concentration: 0.71, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.60 (3H, s), 2.20 - 2.45 (4H, m), 2.45 - 2.65 (4H, m), 2.50 (1H, d, J = 15.0 Hz), 2.86 (1H, d, J = 15.0 Hz), 3.48 (2H, s), 3.89 (1H, d, J = 10.0 Hz), 4.31 (1H, d, J = 10.0 Hz), 7.37 (2H, d, J = 8.0 Hz), 7.50 - 7.56 (3H, m), 7.68 (4H, s).

Using corresponding starting materials gave compounds of Examples 414 to 417 in the same manner as in Example 413.

Example 414

(S)-2-Methyl-6-nitro-2-[4-(4-trifluoromethylbenzyl)-piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 110-112°C.

Example 415

(S)-2-[4-(Biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 182-184°C.

Example 416

(S)-2-Methyl-6-nitro-2-[4-(4-trifluoromethoxybenzyl)-piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 137-138°C.

Example 417

(S)-2-{4-[2-(4-Chlorophenyl)-4-methylthiazol-5-

ylmethyl]piperazin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 174.3-175.5°C.

Example 418

Preparation of (R)-2-[4-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of tert-butyl (R)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazine-1-carboxylate prepared in Example 396 (100 mg, 0.27 mmol) and trifluoroacetic acid (2 ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (5 ml) and neutralized with triethylamine (1 ml, 7.17 mmol), and then the solution was concentrated under reduced pressure. The residue was dissolved in methanol (5 ml). To the solution, 4-phenylbenzaldehyde (149 mg, 0.82 mmol), sodium cyanotrihydroborate (51 mg, 0.82 mmol) and acetic acid (48 μl, 0.82 mmol) were added in this order followed by stirring at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, and the residue was added a saturated sodium hydrogencarbonate solution. The precipitates were filtered off and purified by silica gel column chromatography (ethyl acetate) to afford (R)-2-(biphenyl-4-ylmethyl)piperazin-1-ylmethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (67 mg, yield

57%) as a light yellow powder.

Melting point 112-114°C.

Using corresponding starting materials gave the compound of Example 419 in the same manner as in Example 418.

Example 419

(R)-2-Methyl-6-nitro-2-[4-(4-trifluoromethylbenzyl)-piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 93-95°C.

Example 420

Preparation of (S)-2-chloro-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone

A mixture of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazine-1-carboxylate prepared in Example 393 (1.5 g, 4.1 mmol) and trifluoroacetic acid (20 ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (20 ml), and the solution was added triethylamine (3 ml) and 4-dimethylaminopyridine (100 mg, 0.82 mmol) in this order. To the mixture, a solution of chloroacetyl chloride (0.49 ml, 6.2 mmol) in methylene chloride (2 ml) was added slowly with cooling on ice-bath followed by stirring at room temperature overnight. The reaction mixture was washed with water twice, a saturated sodium hydrogencarbonate solution and a

saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford (S)-2-chloro-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone (600 mg, yield 43%) as a light brown powder.

^{1}H-NMR ($CDCl_3$) δppm:

1.64 (3H, s), 2.50 - 2.70 (3H, m), 2.61 (1H, d, J = 15.0 Hz), 2.70 - 2.90 (1H, m), 2.89 (1H, d, J = 15.0 Hz), 3.15 - 3.55 (3H, m), 3.60 - 3.75 (1H, m), 3.97 (1H, d, J = 10.0 Hz), 4.03 (2H, s), 4.30 (1H, d, J = 10.0 Hz), 7.55 (1H, s).

Example 421

Preparation of (S)-2-(4-chlorophenoxy)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]ethanone

A mixture of (S)-2-chloro-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]ethanone prepared in Example 420 (300 mg, 0.87 mmol), 4-chlorophenol (170 mg, 1.32 mmol), potassium carbonate (180 mg, 1.3 mmol) and DMF (5 ml) was stirred at 60°C for 3 hours. The reaction mixture was allowed to return to room temperature, then diluted with water. The solution was extracted with ethyl acetate twice. The organic phases were combined, washed with a sodium hydroxide solution, water and a

saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from ethanol to afford (S)-2-(4-chlorophenoxy)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone (260 mg, yield 68%) as a light brown powder.

Melting point 179-180°C.

Example 422

Preparation of (S)-2-(4-chlorophenylsulfanyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone

Using a mixture of (S)-2-chloro-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone prepared in Example 420 (300 mg, 0.87 mmol) and 4-chlorothiophenol (190 mg, 1.32 mmol) gave (S)-2-(4-chlorophenylsulfanyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone (80 mg, yield 20%) as a white powder in the same manner as in Example 421.

Melting point 142-145°C.

Example 423

Preparation of (S)-(4-chlorophenyl)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]methanone

A mixture of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-

piperazine-1-carboxylate prepared in Example 393 (300 mg, 0.82 mmol) and trifluoroacetic acid (6 ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (15 ml), and the solution was added triethylamine (2 ml, 14.35 mmol). To the solution, 4-chlorobenzoyl chloride (150.7 mg, 0.86 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 1 hour. The reaction mixture was washed with a saturated sodium hydrogencarbonate solution, water and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was treated with diethyl ether-ethyl acetate to afford (S)-(4-chlorophenyl)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]methanone (282 mg, yield 85%) as a yellow powder. Melting point 173-174°C.

Using corresponding starting materials gave the compound of Example 424 in the same manner as in Example 423.

Example 424

(Biphenyl-4-yl)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]methanone

Melting point 116-118°C.

Example 425

Preparation of [4-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]phenylmethanone

A mixture of 2-(4-tert-butoxycarbonyl-piperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazole prepared in Example 306 (142 mg, 0.39 mmol), trifluoroacetic acid (1 ml) and methylene chloride (1 ml) was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride (2 ml). To the mixture, triethylamine (2 ml, 14.35 mmol) was added. To the solution, benzoyl chloride (54 µl, 0.46 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 1 hour. The reaction mixture was diluted with methylene chloride, washed with a saturated sodium hydrogencarbonate solution, water and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was treated with diethyl ether to afford [4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]phenylmethanone (72 mg, yield 50%) as a yellow powder.

Melting point 145-148.7°C.

Using corresponding starting materials gave compounds of Examples 426 to 433 in the same manner as in Example 425.

Example 426

(4-Chlorophenyl)-[4-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]methanone

Melting point 150.0-155.2°C.

Example 427

[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl](pyridin-4-yl)methanone

^{1}H-NMR ($CDCl_3$) δppm:

1.62 (3H, s), 2.25 - 2.75 (4H, m), 2.61 (1H, d, J = 14.9 Hz), 2.88 (1H, d, J = 14.9 Hz), 3.00 - 3.93 (4H, br), 3.95 (1H, d, J = 9.8 Hz), 4.30 (1H, d, J = 9.8 Hz), 7.26 - 7.55 (2H, m), 7.59 (1H, s), 8.67 - 8.72 (2H, m).

Example 428

1-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-2-phenylethanone

Melting point 175.2-175.9°C.

Example 429

1-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-3-phenylpropan-1-one

Melting point 166.8-169.1°C.

Example 430

1-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-2-phenoxyethanone

Melting point 158-160.6°C.

Example 431

2-(4-Chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone

Melting point 184-187°C.

Example 432

(Biphenyl-4-yl)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]methanone

^{1}H-NMR ($CDCl_3$) δppm:

1.63 (3H, s), 2.45 - 2.80 (4H, m), 2.62 (1H, d, J = 14.9 Hz), 2.90 (1H, d, J = 14.9 Hz), 3.28 - 3.81 (4H, br), 3.95 (1H, d, J = 9.8 Hz), 4.31 (1H, d, J = 9.8 Hz), 7.34 - 7.50 (5H, m), 7.55 (1H, s), 7.56 - 7.63 (4H, m).

Example 433

[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-(4-trifluoromethylphenyl)-methanone

Melting point 161-162°C.

Example 434

Preparation of (S)-[4-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-(4-trifluoromethylphenyl)methanone

(S)-2-Methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydro-chloride prepared in Example 408 (2.36 mg, 0.882 mmol) was suspended in methylene chloride (10 ml). To the suspension, triethylamine (1 ml, 7.17 mmol) was added. To the solution, 4-(trifluoromethyl)benzoyl chloride (193 mg, 0.926 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 1 hour.

The reaction mixture was washed with a saturated sodium hydrogencarbonate solution, water and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-(4-trifluoromethylphenyl)methanone (264 mg, yield 68%) as a white powder.

Melting point 183-184°C.

Using corresponding starting materials gave compounds of Example 435 to 438 in the same manner as in Example 434. (Compounds in Examples 435 to 437 were prepared with 2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 322.)

Example 435

[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-(4-methoxyphenyl)methanone

Melting point 135-137°C.

Example 436

[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-(4-methylphenyl)methanone

Melting point 121-122°C.

Example 437

[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

ylmethyl)piperazin-1-yl]-(3-trifluoromethylphenyl)-methanone

Melting point 122-124°C.

Example 438

(S)-2-(4-Chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone

Melting point 189-190°C.

Example 439

Preparation of (S)-2-(3,4-dichlorophenoxy)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]ethanone

A mixture of 3,4-(dichlorophenoxy)acetic acid (234 mg, 1.06 mmol) and thionyl chloride (5 ml) was stirred under reflux for 30 minutes. The reaction mixture was concentrated under reduced pressure to afford corresponding acid chloride. It was dissolved in methylene chloride (5 ml).

The solution was added to a mixture of (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 (236 mg, 0.88 mmol), methylene chloride (10 ml), and triethylamine (1 ml, 7.17 mmol) with cooling on ice-bath followed by stirring at room temperature for 1 hour. The reaction mixture was washed with a saturated sodium hydrogencarbonate solution, water and a saturated saline solution in this order, dried over sodium sulfate and then filtered.

The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford (S)-2-(3,4-dichlorophenoxy)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]ethanone (183 mg, yield 44%) as a white powder.

Melting point 164-166°C.

Using corresponding starting materials gave the compound of Example 440 in the same manner as in Example 439.

Example 440

(S)-1-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-4-(4-trifluoro-methylphenyl)butan-1-one

Melting point 145-146°C.

Example 441

Preparation of (S)-3-(4-chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]propenone

A mixture of 4-chlorocinnamic acid (300 mg, 1.64 mmol), 1-hydroxybenzotriazole (HOBT) (240 mg, 1.77 mmol), WSCD (350 mg, 1.83 mmol) and methylene chloride (10 ml) stirred at room temperature for 30 minutes was added a mixture of (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydro-chloride prepared in Example 408 (434 mg, 1.64 mmol), methylene chloride (10 ml), and triethylamine (3.3 ml,

2.37 mmol) with cooling on ice-bath followed by stirring at room temperature for 3 hours. The reaction mixture was washed with a saturated sodium hydrogencarbonate solution, water and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate) to afford (S)-3-(4-chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]propenone (180 mg, yield 26%) as a white powder.

Melting point 220-222°C.

Using corresponding starting materials gave compounds of Examples 442 to 445 in the same manner as in Example 441.

Example 442

(S)-3-(Chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]propan-1-one

Melting point 177-178°C.

Example 443

(S)-4-(4-Chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]butan-1-one

Melting point 146-147°C.

Example 444

(S)-3-(3,4-Dichlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]propenone

Melting point 213-215°C.

Example 445

(S)-5-(4-Chlorophenyl)-1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]pentan-1-one

Melting point 108-111°C.

Example 446

Preparation of 1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-2-(4-tolyl)ethanone

A mixture of 2-Methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 322 (240 mg, 0.79 mmol), DMF (5 ml) and triethylamine (0.22 ml, 1.58 mmol) was added p-tolylacetic acid (140 mg, 0.93 mmol) and WSCD (180 mg, 0.93 mmol) in this order followed by stirring at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with water twice, a saturated sodium hydrogencarbonate solution and a saturated saline solution in this order, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was treated with diethylether to afford 1-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-2-(4-tolyl)ethanone (172 mg, yield 64%) as a white powder.

Melting point 213-214°C.

Using corresponding starting materials gave the compound of Example 447 in the same manner as in Example 446.

Example 447

(4-Dimethylaminophenyl)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]methanone

Melting point 204-207°C.

Example 448

Preparation of (S)-2-{4-[3-(4-Chlorophenyl)propane-1-sulfonyl]piperazin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazine-1-carboxylate prepared in Example 393 (300 mg, 0.82 mmol) and trifluoroacetic acid (10 ml) was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride (10 ml). To the solution, triethylamine (3 ml, 21.52 mmol) was added followed by stirring at room temperature for 10 minutes, and then 3-(4-chlorophenyl)propane-1-sulfonyl chloride (300 mg, 1.19 mmol) was added followed by stirring at room temperature for 3 days. The reaction mixture was washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under

reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford (S)-2-{4-[3-(4-chlorophenyl)propane-1-sulfonyl]piperazin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (330 mg, yield 84%) as a white powder.

Melting point 150-151°C.

Using 2-(4-tert-butoxycarbonylpiperazin-1-ylmethyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 306 gave compounds of Examples 449 and 450 in the same manner as in Example 448.

Example 449

2-[4-(4-Chlorobenzenesulfonyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 202-204°C.

Example 450

2-[4-(4-Chlorophenylmethanesulfonyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 215-217°C.

Example 451

Preparation of (S)-2-{4-[2-(4-chlorophenyl)ethane-sulfonyl]piperazin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of(S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 (236 mg, 0.88

mmol) and DMF (3 ml) was added potassium carbonate (500 mg, 3.62 mmol) and 2-(4-chlorophenyl)ethanesulfonyl chloride (240 mg, 1 mmol) in this order followed by stirring at room temperature overnight. To the reaction mixture, water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with water three times and saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford (S)-2-{4-[2-(4-chlorophenyl)ethanesulfonyl]piperazin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (100 mg, yield 26%) as a white powder.

Melting point 192-193°C.

Using (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 gave compounds of Examples 452 to 454 in the same manner as in Example 451. Also, using 2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 322 gave the compound of Example 455 in the same manner as in Example 451.

Example 452

(S)-2-[4-(4-Chlorobenzenesulfonyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazole

Melting point 216-218°C.

Example 453

(S)-2-[4-(4-Chlorophenylmethanesulfonyl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 204-206°C.

Example 454

(S)-2-{4-[4-(4-Chlorophenyl)butane-1-sulfonyl]-piperazin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazole

Melting point 176-177°C.

Example 455

2-{4-[2-(4-Chlorophenyl)ethanesulfonyl]piperazin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 182-184°C.

Example 456

Preparation of 4-trifluoromethylbenzyl (S)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

A mixture of tert-butyl (S)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 394 (300 mg, 0.84 mmol) and methylene chloride (2 ml) was added trifluoroacetic acid (1 ml) followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved

in DMF (1 ml) and neutralized with triethylamine (1 ml).

To the solution, a mixture of 4-(trifluoromethyl)benzyl alcohol (297 mg, 1.69 mmol), DMF (1 ml), and 1,1'-carbonyldiimidazole (274 mg, 1.69 mmol) stirred at room temperature for 1 hour was added followed by stirring at room temperature for 3 hours. To the reaction mixture, water was added, and the solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water twice and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford 4-trifluoromethylbenzyl (S)-4-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (273 mg, yield 71%) as a white powder. $[\alpha]_D^{28}$ = -14.851° (concentration: 0.404, $CHCl_3$) Melting point 125-125.5°C.

Example 457

Preparation of 4-trifluoromethylbenzyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazine-1-carboxylate

A mixture of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 393 (1.87 g, 5.09 mmol) and methylene chloride (20 ml)

was added trifluoroacetic acid (20 ml) followed by stirring for 5 minutes, and then concentrated under reduced pressure. The residue was dissolved in DMF (20 ml). To the solution, a mixture of 1,1'-carbonyldiimidazole (1.76 g, 10.9 mmol), 4-(trifluoromethyl)benzyl alcohol (1.92 g, 10.9 mmol) and DMF (20 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature overnight. The reaction mixture was extracted with ethyl acetate. The organic phases were combined, washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/acetone = 3/1), recrystallized from isopropyl alcohol. The resulting solids were filtered off and then dried under reduced pressure to afford 4-trifluoromethylbenzyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (1.48 g, yield 53%) as a light yellow powder.

Melting point 140.4-141.6°C

Optical purity 99.9% e.e.

^{1}H-NMR ($CDCl_3$) δppm:

1.62 (3H, s), 2.52 - 2.69 (5H, m), 2.88 (1H, d, J = 14.9 Hz), 3.43 (4H, br), 3.93 (1H, d, J = 9.7 Hz), 4.28 (1H, d, J = 9.7 Hz), 5.16 (2H, s), 7.44 (2H, d, J = 8.1 Hz), 7.53 (1H, s), 7.61 (2H, d, J = 8.1 Hz).

Example 458

Preparation of 1,3,3-trimethyl-2-oxo-2,3-dihydro-1H-indol-5-ylmethyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

To a mixture of 3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-5-ylmethyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (300 mg, 0.62 mmol) and DMF (3 ml), sodium hydride (27 mg, 0.68 mmol) was added followed by stirring for 30 minutes with cooling on ice-bath. To the reaction mixture, methyl iodide (97 mg, 0.68 mmol) was added followed by stirring at room temperature for 2 hours. To the reaction mixture, water was added, and the mixture was extracted with ethyl acetate twice. The organic phases were combined, washed with water twice and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate) to afford 1,3,3-trimethyl-2-oxo-2,3-dihydro-1H-indol-5-ylmethyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (140 mg, 45%) as a light yellow powder. Melting point 80-100°C (decomposition).

Using corresponding starting materials gave the compound of Example 459 in the same manner as in Example 458.

Example 459

1-Methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylmethyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Melting point 189-190°C.

Example 460

Preparation of 3,5-dichlorobenzyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazine-1-carboxylate

To a mixture of (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 (300 mg, 0.88 mmol) and DMF (3 ml), triethylamine (270 mg, 2.67 mmol) was added for neutralization. To the solution, a mixture of 3,5-dichlorobenzyl alcohol (180 mg, 1.02 mmol), DMF (3 ml) and 1,1'-carbonyldiimidazole (180 mg, 1.11 mmol) stirred at room temperature for 2 hours was added followed by stirring at room temperature overnight. To the reaction mixture, water was added, and the mixture was extracted with ethyl acetate twice. The organic phases were combined, washed with water twice and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate) to afford 3,5-dichlorobenzyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (220 mg, yield 53%)

as a white powder.

Melting point 129-130°C.

Example 461

Preparation of 3-(3-trifluoromethylphenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate maleate

Using tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 393 (1.09 g, 2.97 mmol) gave 3-(3-trifluoromethylphenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate maleate (945 mg, 63%) as a white powder in the same manner as in Example 344.

Melting point 136-138°C.

Using corresponding starting materials gave compounds of Examples 462 to 465 in the same manner as in Example 461.

Example 462

[(E)-3-Methyl-3-(3-trifluoromethylphenyl)]-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate maleate

Melting point 142-143°C.

Example 463

3-(3-Chlorophenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate maleate

Melting point 150-151°C.

Example 464

3-(2,4,6-Trifluorophenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazine-1-carboxylate maleate

Melting point 158-159°C.

Example 465

[(Z)-3-Methyl-3-(3-trifluoromethylphenyl)]-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate maleate

Melting point 124-125°C.

Example 466

Preparation of 4-fluorobenzyl (R)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

Using tert-butyl (R)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 396 (106 mg, 0.29 mmol) gave 4-fluorobenzyl (R)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (79 mg, yield 66%) as a white powder in the same manner as in Example 457.

$[\alpha]_D^{28}$ = 19.70° (concentration: 1.066, $CHCl_3$)

Melting point 167-169°C.

Example 467

Preparation of (S)-4-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid [3-(4-trifluoromethylphenyl)-2-propenyl]amide

A mixture of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

ylmethyl)piperazine-1-carboxylate prepared in Example 393 (926 mg, 2.52 mmol), trifluoroacetic acid (10 ml) and methylene chloride (3 ml) was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in DMF (3 ml) and neutralized with triethylamine (2 ml, 14.35 mmol). To the solution, a mixture of 3-(4-trifluoromethylphenyl)-2-propenylamine (761 mg, 3.78 mmol), 1,1'-carbonyldiimidazole (613 mg, 3.78 mmol) and DMF (3 ml) stirred at room temperature overnight was added followed by stirring at room temperature overnight. To the reaction mixture, water was added followed by extraction with ethyl acetate. The extract was washed with water three times and a saturated saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid [3-(4-trifluoromethylphenyl)-2-propenyl]amide (1.2 g, yield 96%) as a light yellow powder.

Melting point 105-107°C.

Using 2-(4-tert-butoxycarbonylpiperazin-1-yl)methyl-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 306 gave compounds of Examples 468 to 470 in the same manner as in Example

467.

Example 468

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-trifluoromethylbenzyl)amide

Melting point 201-202.5°C.

Example 469

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-trifluoromethylphenyl)amide

Melting point 216-217°C.

Example 470

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-chloro-3-trifluoromethylphenyl)amide

Melting point 222-224°C.

Example 471

Preparation of (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid cyclohexylamide

(S)-2-Methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 (236 mg, 0.88 mmol) was dissoloved in a mixture of methylene chloride (15 ml) and triethylamine (2 ml, 14.35 mmol). To the solution, cyclohexyl isocyanate (120 mg, 0.96 mmol) was added followed by stirring at room temperature for 1 hour. The reaction mixture was

washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid cyclohexylamide (164 mg, 47%) as a light yellow powder.
Melting point 98-101°C.

Using 2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 322 gave compounds of Examples 472 to 476 in the same manner as in Example 471.

Example 472

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-methoxyphenyl)amide

Melting point 167-168°C.

Example 473

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-chlorophenyl)-amide

Melting point 185-188°C (decomposition).

Example 474

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (3-trifluoromethylphenyl)amide

Melting point 183-184°C.

Example 475

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (3,4-dichlorophenyl)amide

Melting point 212-214°C (decomposition).

Example 476

4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-methylphenyl)-amide

Melting point 202-203°C (decomposition).

Example 477

Preparation of (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-trifluoromethylphenyl)amide

(S)-2-Methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 (236 mg, 0.88 mmol) was dissolved in a mixture of methylene chloride (5 ml) and triethylamine (2 ml, 14.35 mmol). To the solution, a mixture of 4-aminobenzotrifluoride (142 mg, 0.882 mmol), 1,1'-carbonyldiimidazole (143 mg, 0.882 mmol) and DMF (6 ml) stirred at room temperature overnight was added followed by stirring at room temperature for 6 hours. To the reaction mixture, water was added, and the mixture was extracted with ethyl acetate. The organic phase was washed with water three times and a saturated saline solution, dried over sodium sulfate

and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 30/1) to afford (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-trifluoromethylphenyl)amide (90 mg, yield 23%) as a white powder.

Melting point 150-152.5°C.

Using corresponding starting materials gave compounds of Examples 478 to 481 in the same manner as in Example 477.

Example 478

(S)-4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-methoxyphenyl)amide

Melting point 185.5-187.5°C.

Example 479

(S)-4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-trifluoromethylbenzyl)amide

Melting point 101-103.6°C.

Example 480

(S)-4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-chlorophenyl)amide

Melting point 156-159°C (decomposition).

Example 481

(S)-4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-methylphenyl)amide

Melting point 207-210°C (decomposition).

Example 482

Preparation of (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid N-methyl-N-(4-trifluoromethylphenyl)amide

A mixture of (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid (4-trifluoromethylphenyl)amide prepared in Example 477 (200 mg, 0.44 mmol), DMF (4 ml), and sodium hydride (26 mg, 0.66 mmol) was stirred at room temperature for 1.5 hours. To the mixture, methyl iodide (0.5 ml, 0.76 mmol) was added followed by stirring at room temperature overnight. To the reaction mixture, water was added, and the mixture was extracted with ethyl acetate. The organic phase was washed with water three times and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) to afford (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylic acid N-methyl-N-(4-trifluoromethylphenyl)amide (35 mg, yield 17%) as a white powder.

Melting point 100.4-102.4°C.

Example 483

Preparation of (S)-[4-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-[4-(4-trifluoromethylphenyl)piperidin-1-yl]methanone

A mixture of tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazine-1-carboxylate prepared in Example 393 (1.17 g, 3.32 mmol), trifluoroacetic acid (5 ml) and methylene chloride (10 ml) was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride (10 ml). To the resulting solution, triethylamine (5 ml, 35.87 mmol) was added followed by stirring at room temperature for 10 minutes. The solution was concentrated under reduced pressure, the residue was dissolved in DMF (15 ml). To the mixture, potassium carbonate (920 mg, 6.64 mmol) and a solution of 4-(4-trifluoromethylphenyl)-piperidine-1-carbonylchloride (1.07 g, 3.65 mmol) in DMF (10 ml) was added slowly with cooling on ice-bath followed by stirring at room temperature overnight. To the reaction mixture, water was added followed by extraction with ethyl acetate. The extract was washed with water three times and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 30/1) to

afford (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-[4-(4-trifluoromethylphenyl)piperidin-1-yl]methanone (575 mg, yield 33%) as a white powder.

Melting point 179.1-181.9°C.

Example 484

Preparation of (S)-[4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridin-1-yl]-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]methanone

A mixture of (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 (401 mg, 1.5 mmol), DMF (8 ml) and potassium carbonate (750 mg, 5.4 mmol) was stirred at room temperature for 10 minutes. To the reaction mixture, a solution of 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine-1-carbonylchloride (400 mg, 1.56 mmol) in DMF (3 ml) was added slowly with cooling on ice-bath followed by stirring at room temperature overnight. To the reaction mixture, water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with water three times and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from ethanol to afford (S)-[4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridin-1-yl]-[4-(2-methyl-6-nitro-2,3-

dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]methanone (380 mg, yield 53%) as a light yellow powder.

Melting point 161-162°C.

Using (S)-2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 408 gave compounds of Examples 485 and 486 in the same manner as in Example 484. Also, using 2-methyl-6-nitro-2-(piperazin-1-ylmethyl)-2,3-dihydroimidazo[2,1-b]oxazole dihydrochloride prepared in Example 322 gave the compound of Example 487 in the same manner as in Example 484.

Example 485

(S)-[4-(4-Chlorophenyl)pyridin-1-yl]-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]methanone

Melting point 156-159°C.

Example 486

(S)-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-[4-(4-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridin-1-yl]methanone

Melting point 168.4-171.7°C.

Example 487

[4-(4-Chlorophenyl)piperidin-1-yl]-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]methanone

Melting point 186-187°C.

Example 488

Preparation of (S)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]benzoic acid

Tert-butyl (S)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]benzoate (300 mg, 0.68 mmol) in triluoroacetic acid (10 ml) was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, neutralized with triethylamine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1), crystallized from methanol-diisopropyl ether to afford (S)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]benzoic acid (186 mg, yield 71%) as a white powder.
MS 387(M^+)
Melting point 248-252°C.

Example 489

Preparation of (S)-2-[4-(2,6-diphenylpyrimidin-4-yl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Tert-butyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate prepared in Example 393 (500 mg, 1.36 mmol) was dissolved in methylene chloride (2 ml). To the solution, trifluoroacetic acid (10 ml) was added followed by stirring at room temperature for 3 hours.

The reaction mixture was concentrated under reduced pressure, and added methylene chloride (4 ml) and triethylamine (4 ml). The reaction mixture was stirred at room temperature for 5 minutes and then concentrated under reduced pressure, and the residue was dissolved in DMF (5 ml). To the solution, 4-chloro-2,6-diphenylpyrimidine (400 mg, 1.50 mmol) and DBU (0.2 ml, 1.36 mmol) were added followed by stirring at 100°C for 5 hours. The reaction mixture was allowed to return to room temperature, poured into water, and then the mixture was extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from methylene chloride-diisopropyl ether to afford (S)-2-[4-(2,6-diphenylpyrimidin-4-yl)piperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (113 mg, yield 17%) as a white powder.

MS 498$(M+H)^+$

Melting point 202.5-205.4°C.

Using corresponding starting materials gave the compound of Example 490 in the same manner as in Example 489.

Example 490

(S)-2-[4-(4,6-Diphenylpyrimidin-2-yl)piperazin-1-

ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 7%, melting point 201.2-205.4°C.

Example 491

Preparation of tert-butyl {4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate

2-Chloro-4-nitro-1H-imidazole (2.05 g, 13.9 mmol), tert-butyl 4-(2-methyloxiran-2-ylmethyl)-piperazin-1-yl)carbamate (3.14 g, 11.6 mmol) and sodium hydrogencarbonate (1.46 g, 17.4 mmol) in 1-propanol (13 ml) were stirred under heating for 6 hours. The reaction mixture was extracted with ethyl acetate twice. The organic phases were combined, washed with a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/acetone = 2/1) to afford tert-butyl {4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate (1.55 g, yield 32%) as a white powder.

^{1}H-NMR ($CDCl_3$) δppm:

1.12 (3H, s), 1.46 (9H, s), 2.36 (1H, d, J = 13.9 Hz), 2.50 (1H, d, J = 13.9 Hz), 2.64 - 2.84 (8H, m), 3.32 (1H, s), 3.96 (2H, s), 5.46 (1H, br), 8.03 (1H, s).

Example 492

Preparation of tert-butyl {4-[3-(2-chloro-4-

nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate (alternative synthesis of the compound of Example 491)

Using 2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 6 (4.36 g, 20.0 mmol) and tert-butyl piperazin-1-ylcarbamate (4.44 g, 22.0 mmol) gave tert-butyl {4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate (6.08 g, yield 72%) as a white powder in the same manner as in Example 365.

Example 493

Preparation of tert-butyl [4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate

Using tert-butyl {4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate prepared in Example 492 (6.87 g, 16.4 mmol) gave tert-butyl [4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate (2.71 g, yield 43%) as a white powder in the same manner as in Example 393.

^{1}H-NMR ($CDCl_3$) δppm:

1.43 (9H, s), 1.60 (3H, s), 2.36 (1H, d, J = 14.0 Hz), 2.52 - 2.90 (9H, m), 3.90 (1H, d, J = 9.7 Hz), 4.27 (1H, d, J = 9.7 Hz), 5.35 (1H, br), 7.53 (1H, s).

Example 494

Preparation of benzyl [4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-

yl]carbamate

A mixture of tert-butyl [4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate prepared in Example 493 (150 mg, 0.39 mmol) and trifluoroacetic acid (4 ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methylene chloride (4 ml) and neutralized with triethylamine (4 ml, 28.7 mmol). Subsequently, to the solution, benzyl chloroformate (100 mg, 0.59 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 2 hours. To the reaction mixture, a saturated sodium hydrogencarbonate solution was added. The mixture was extracted with methylene chloride. The extract was washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/acetone = 1/1) to afford benzyl [4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate (6.5 mg, yield 4%) as a light yellow powder.

^{1}H-NMR ($CDCl_3$) δppm:

1.60 (3H, s), 2.53 - 2.90 (10H, m), 3.89 (1H, d, J = 9.6 Hz), 4.27 (1H, d, J = 9.6 Hz), 5.11 (2H, s), 5.88 (1H, br), 7.25 - 7.34 (5H, m), 7.52 (1H, s).

Example 495

Preparation of N-[4-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethoxybenzylidene)amine

A mixture of tert-butyl [4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate prepared in Example 493 (40 mg, 0.11 mmol), 4-trifluoromethoxybenzaldehyde (24 mg, 0.13 mmol), trifluoroacetic acid (0.08 ml) and methylene chloride (1 ml) was stirred at room temperature for 3 hours. The mixture was added a saturated sodium hydrogencarbonate solution for neutralization followed by extraction with methylene chloride. The solution was washed with water and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 3/1) to afford N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethoxybenzylidene)amine (19 mg, yield 40%) as a white powder.

Melting point 189.2-190.9°C.

Example 496

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-{4-[(4-trifluoromethylbenzylidene)amino]-piperazin-1-yl}propan-2-ol

A mixture of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12

(218 mg, 1 mmol), N-(piperazin-1-yl)-N-(4-trifluoromethylbenzylidene)amine (283 mg, 1.1 mmol) and DMF (2 ml) was stirred at 70-80°C for 7 hours. The reaction mixture was allowed to return to room temperature and then added water, and the resulting solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water 3 times and a saturated saline solution, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/acetone = 1/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-{4-[(4-trifluoromethylbenzylidene)amino]piperazin-1-yl}propan-2-ol (402 mg, yield 85%) as a light yellow powder.

$[\alpha]_D^{27}$ = 19.01° (concentration: 1.010, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.18 (3H, s), 2.42 (1H, d, J = 13.9 Hz), 2.57 (1H, d, J = 13.9 Hz), 2.71 - 2.95 (4H, m), 3.10 - 3.33 (5H, m), 4.02 (2H, s), 7.51 (1H, s), 7.58 (2H, d, J = 8.4 Hz), 7.68 (2H, d, J = 8.4 Hz), 8.05 (1H, s).

Example 497

Preparation of tert-butyl (S)-{4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate

Using (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (29.8 g, 137 mmol) and tert-butyl piperazin-1-ylcarbamate

(28.9 g, 144 mmol) gave tert-butyl (S)-{4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate (36.68 g, yield 64%) as a white powder in the same manner as in Example 496.

$[\alpha]_D^{27}$ = 17.793° (concentration: 1.006, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.12 (3H, s), 1.45 (9H, s), 2.36 (1H, d, J = 14.0 Hz), 2.50 (1H, d, J = 14.0 Hz), 2.64 - 2.84 (8H, m), 3.32 (1H, s), 3.97 (2H, s), 5.47 (1H, br), 8.04 (1H, s).

Using corresponding starting materials gave compounds of Examples 498 to 500 in the same manner as in Example 497.

Example 498

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-2-methyl-3-{4-[(4-trifluoromethoxybenzylidene)amino]piperazin-1-yl}propan-2-ol

$[\alpha]_D^{27}$ = 12.326° (concentration: 1.006, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.17 (3H, s), 2.41 (1H, d, J = 13.9 Hz), 2.56 (1H, d, J = 13.9 Hz), 2.71 - 2.95 (4H, m), 3.14 - 3.29 (5H, m), 4.01 (2H, s), 7.19 (2H, d, J = 8.0 Hz), 7.50 (1H, s), 7.62 (2H, d, J = 8.0 Hz), 8.05 (1H, s).

Example 499

(S)-1-(2-Chloro-4-nitroimidazol-1-yl)-2-methyl-3-{4-[(5-trifluoromethylbenzofuran)-2-ylmethylene)amino]-piperazin-1-yl}propan-2-ol

^{1}H-NMR ($CDCl_3$) δppm:

1.18 (3H, s), 2.43 (1H, d, J = 14.0 Hz), 2.58 (1H, d, J = 14.0 Hz), 2.73 - 2.82 (2H, m), 2.86 - 2.95 (2H, m), 3.17 (1H, s), 3.31 (4H, s), 4.03 (2H, s), 6.82 (1H, s), 7.46 (1H, s), 7.52 (1H, d, J = 8.7 Hz), 7.59 (1H, d, J = 8.7 Hz), 7.83 (1H, s), 8.05 (1H, s).

Example 500

(S)-1-{4-[(5-Chlorobenzofuran)-2-ylmethylene)amino]-piperazin-1-yl}-3-(2-chloro-4-nitroimidazol-1-yl)-2-methylpropan-2-ol

^{1}H-NMR ($CDCl_3$) δppm:

1.18 (3H, s), 2.42 (1H, d, J = 14.0 Hz), 2.57 (1H, d, J = 14.0 Hz), 2.71 - 3.00 (4H, m), 3.17 (1H, s), 3.23 - 3.38 (4H, m), 4.02 (2H, s), 6.71 (1H, s), 7.22 (1H, dd, J = 2.1 Hz, 8.7 Hz), 7.33 - 7.43 (2H, m), 7.50 (1H, d, J = 2.1 Hz), 8.05 (1H, s).

Example 501

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenylamino)piperazin-1-yl]propan-2-ol

Using (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.610 g, 2.82 mmol) and N-(piperazin-1-yl)-4-trifluoromethylaniline (0.760 g, 3.09 mmol) gave (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenylamino)piperazin-1-yl]propan-2-ol (1.125 g, yield 86%) as a colorless solid in the same manner as in Example 496.

^{1}H-NMR ($CDCl_3$) δppm:

1.15 (3H, s), 2.39 (1H, d, J = 14.0 Hz), 2.54 (1H, d, J = 14.0 Hz), 2.60 - 2.95 (8H, m), 3.25 (1H, s), 3.99 (2H, s), 4.67 (1H, s), 6.90 (2H, d, J = 8.6 Hz), 7.43 (2H, d, J = 8.6 Hz), 8.04 (1H, s).

Example 502

Preparation of (S)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-4-trifluoromethylaniline

Using (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-[4-(4-trifluoromethylphenylamino)piperazin-1-yl]propan-2-ol prepared in Example 501 (1.125 g, 2.43 mmol) gave (S)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-4-trifluoromethylaniline (0.715 g, yield 69%) as a white solid in the same manner as in Example 493.

Melting point 192.1-195.3°C.

Example 503

Preparation of tert-butyl (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate

Using tert-butyl (S)-{4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}carbamate prepared in Example 497 (36.68 g) gave tert-butyl (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate (19.51 g, yield 58%) as a white powder in the same manner as in Example 493.

Optical purity >99.5% e.e.

$[\alpha]_D^{27}$ = 9.84° (concentration: 1.016, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.43 (9H, s), 1.60 (3H, s), 2.35 (1H, d, J = 14.0 Hz), 2.52 - 2.92 (9H, m), 3.89 (1H, d, J = 9.7 Hz), 4.27 (1H, d, J = 9.7 Hz), 5.35 (1H, s), 7.53 (1H, s).

Example 504

Preparation of (S)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethylbenzylidene)amine

To a mixture of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-3-{4-[(4-trifluoromethylbenzylidene)amino]piperazin-1-yl}propan-2-ol prepared in Example 496 (847 mg, 0.85 mmol) and DMF (4 ml), sodium hydride (69 mg, 1.73 mmol) was added followed by stirring for 2.5 hours with cooling on ice-bath. To the reaction mixture, water was added, and the precipitates were filtered off. The resulting solid was washed with methanol and recrystallized from acetone/water to afford (S)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethylbenzylidene)amine (248 mg, yield 69%) as a light yellow powder.

Melting point 201-202.3°C (decomposition)

Optical purity >99.5% e.e.

$[\alpha]_D^{27}$ = -64.64° (concentration: 1.018, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.64 (3H, s), 2.55 - 2.79 (3H, m), 2.80 - 3.20 (7H, m), 3.94 (1H, d, J = 9.7 Hz), 4.33 (1H, d, J = 9.7 Hz),

7.44 (1H, s), 7.48 - 7.67 (5H, m).

Using corresponding starting materials gave compounds of Examples 505 to 507 in the same manner as in Example 504.

Example 505

(S)-N-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethylbenzylidene)amine

Melting point 188.4-191.2°C

Optical purity >99.0% e.e.

$[\alpha]_D^{27}$ = -58.30° (concentration: 1.024, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.64 (3H, s), 2.55 - 2.77 (3H, m), 2.82 - 3.18 (7H, m), 3.94 (1H, d, J = 9.7 Hz), 4.33 (1H, d, J = 9.7 Hz), 7.16 (2H, d, J = 8.2 Hz), 7.43 (1H, s), 7.55 (1H, s), 7.58 (2H, d, J = 8.2 Hz).

Example 506

(S)-N-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(5-trifluoromethylbenzofuran-2-ylmethylene)amine

Melting point 190.2-191.8°C

Optical purity 99.8% e.e.

$[\alpha]_D^{27}$ = -81.05° (c = 0.992, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) δppm:

1.64 (3H, s), 2.59 - 2.77 (3H, m), 2.86 - 3.00 (3H, m), 3.05 - 3.26 (4H, m), 3.96 (1H, d, J = 9.7 Hz), 4.33 (1H, d, J = 9.7 Hz), 6.79 (1H, s), 7.39 (1H, s), 7.41 - 7.57 (3H, m), 7.82 (1H, s).

Example 507

(S)-N-(5-Chlorobenzofuran-2-ylmethylene)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine

Optical purity >99.0% e.e.

$[\alpha]_D^{27}$ = -84.48° (concentration: 1.018, $CHCl_3$)

Melting point 213.8-215.7°C

^{1}H-NMR ($CDCl_3$) δppm:

1.63 (3H, s), 2.57 - 2.76 (3H, m), 2.81 - 2.95 (3H, m), 3.00 - 3.24 (4H, m), 3.94 (1H, d, J = 9.7 Hz), 4.32 (1H, d, J = 9.7 Hz), 6.67 (1H, s), 7.17 - 7.23 (1H, m), 7.30 - 7.43 (2H, m), 7.48 (1H, d, J = 2, 1 Hz), 7.53 (s, 1H).

Example 508

Preparation of (S)-N-(5-chlorobenzofuran-2-ylmethylene)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine (alternative synthesis of the compound of Example 507)

To a mixture of tert-butyl (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]carbamate prepared in Example 503 (0.20 g, 0.523 mmol) and 5-chlorobenzofuran-2-carbaldehyde (0.113 g, 0.628 mmol) and methylene chloride (4 ml), trifluoroacetic acid (0.4 ml) was added followed by stirring at room temperature for 2 hours. To the reaction mixture, a saturated sodium hydrogencarbonate solution was added followed by

extraction with methylene chloride. The organic phase was washed with a saturated saline solution, dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 4/1) to afford (S)-N-(5-chlorobenzofuran-2-ylmethylene)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine (0.137 g, yield 59%) as a light yellow powder.

Example 509

Preparation of (S)-N-[1-(4-chlorophenyl)ethylidene]-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine

A mixture of tert-butyl (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]carbamate prepared in Example 503 (200 mg, 0.52 mmol), trifluoroacetic acid (2 ml) and methylene chloride (4 ml) was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride (4 ml) and then neutralized with triethylamine (4 ml, 28.7 mmol). To the neutralized solution, a solution of 4-chloroacetophenone (97 mg, 0.63 mmol) in ethanol (4 ml) was added followed by stirring under reflux for 4 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced

pressure. The residue was purified by silica gel column chromatography (n-hexane/acetone = 3/1) to afford (S)-N-[1-(4-chlorophenyl)ethylidene]-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine (39 mg, yield 18%) as a light yellow powder.

Melting point 164.6-166.5°C

Using corresponding starting materials gave compounds of Examples 510 to 513 in the same manner as in Example 509.

Example 510

(S)-N-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-[1-(4-trifluoromethylphenyl)ethylidene]amine

Melting point 167.9-169.4°C

Example 511

(S)-N-[4-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-[1-(4-trifluoromethoxyphenyl)ethylidene]amine

Melting point 177.8-180.1°C

Example 512

(S)-N-Cyclohexylidene-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine

Melting point 178.6-179.3°C

Example 513

N-(2-Benzylideneheptylidene)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-

yl]amine

Melting point 166.6-169.6°C.

Example 514

Preparation of (S)-N-[4-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethylbenzyl)amine

To a mixture of (S)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethylbenzylidene)amine prepared in Example 504 (100 mg, 0.23 mmol) and THF (4 ml), sodium borohydride (13 mg, 0.34 mmol) was added with cooling on ice-bath followed by stirring at room temperature for 30 minutes. To the reaction mixture, methanol (1 ml) was added, and the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 2/1) to afford (S)-N-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]-N-(4-trifluoromethylbenzyl)amine (32 mg, yield 31%) as a light yellow powder.

Melting point 131.3-135.5°C.

Example 515

Preparation of (S)-[4-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine dihydrochloride

A mixture of tert-butyl (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]carbamate prepared in Example 503 (300

mg, 0.78 mmol), concentrated hydrochloric acid (2 ml) and methanol (4 ml) was stirred at 50°C for 30 minutes. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. The residue was recrystallized from methanol/ether to afford (S)-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]amine dihydrochloride (265 mg, yield 91%) as a yellow powder. Melting point 176°C (decomposition).

Example 516

Preparation of 3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one

To a suspension of 2-chloro-4-nitro-1H-imidazole (2.21 g, 14.98 mmol) and 3-(2-methyloxiran-2-ylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (2.37 g, 7.49 mmol) in ethanol (25 ml), sodium hydrogencarbonate (1.32 g, 15.73 mmol) was added followed by stirring under reflux for 8 hours. To the reaction mixture, water was added, and the mixture was extracted with methylene chloride. The organic phase was dried over magnesium sulfate, and concentrated under reduced pressure to afford 3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (3.27 g, yield 94%) as a light yellow amorphous form.

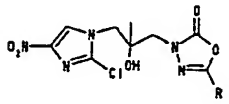
^{1}H-NMR (DMSO-d_6) δppm:

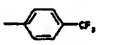
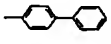
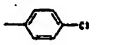
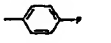
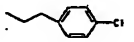
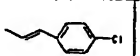
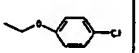
1.53 (3H, s), 3.67 (1H, d, J = 8.8 Hz), 3.81 (1H, d, J

= 8.8 Hz), 4.49 (2H, s), 7.42 - 7.66 (2H, m), 7.86 - 8.09 (2H, m), 8.54 (1H, s), 10.98 (1H, br).

Using corresponding starting materials gave compounds of Examples 517 to 523 shown in the following table in the same manner as in Example 516.

Table 18



Example	R	^{1}H NMR δ		Yield (%)
517		$CDCl_3$	1.59(3H, s), 3.78(1H, d, J=8.5Hz), 3.86(1H, d, J=8.5Hz), 4.29(1H, d, J=15.1Hz), 4.57(1H, d, J=15.1Hz), 7.61(2H, d, J=8.1Hz), 7.79(2H, d, J=8.1Hz), 8.06(1H, s), 9.17(1H, br).	70
518		$CDCl_3$	1.61(3H, s), 3.79 (1H, d, J=8.5Hz), 3.85(1H, d, J=8.5Hz), 4.27(1H, d, J=15.0Hz), 4.56(1H, d, J=15.0Hz), 7.33-7.63 (7H, m), 7.78(2H, d, J=8.4Hz), 8.06(1H, s), 9.02(1H, br).	82
519		$CDCl_3$	1.62(3H, s), 3.75(1H, d, J=8.5Hz), 3.83(1H, d, J=8.5Hz), 4.27(1H, d, J=15.0Hz), 4.54(1H, d, J=15.0Hz), 7.34(2H, dd, J=1.8Hz, 8.6Hz), 7.63(2H, dd, J=1,8Hz, 8.6Hz), 8.03(1H, s), 9.05(1H, br).	57
520		DMSO-d_6	1.51(3H, s), 3.66(1H, d, J=8.8Hz), 3.79(1H, d, J=8.8Hz), 4.48(2H, s), 7.24-7.41(2H, m), 7.84-7.96(2H, m), 8.52(1H, s).	64
521		$CDCl_3$	1.56(3H, s), 2.41-2.53(2H, m), 2.81-3.00(2H, m), 3.56(1H, d, J=8.5Hz), 3.63(1H, d, J=8.5Hz), 4.22(1H, d, J = 15.0Hz), 4.42(1H, d, J=15.0Hz), 7.12(2H, d, J=8.4Hz), 7.26(2H, d, J=8.4Hz), 7.55(1H, br), 7.97(1H, s).	92
522		DMSO-d_6	1.53(3H, s), 3.63(1H, d, J=8.8Hz), 3.77(1H, d, J=8.8Hz), 4.43(1H, d, J =15.0Hz), 4.51(1H, d, J=15.0Hz), 6.58(1H, d, J=15.9Hz), 7.43-7.55(3H, m), 7.64(2H, d, J =8.5Hz), 7.51(1H, s).	89
523		$CDCl_3$	1.56(3H, s), 3.72(2H, s) , 4.25(1H, d, J=15.1Hz), 4.44(1H, d, J=15.1Hz), 4.59(2H, s), 6.85(2H, dd, J=2.3Hz, 6.8Hz), 7.29(2H, dd, J=2.3Hz 6.8Hz), 7.98(1H, s), 8.49 (1H, br).	98

Example 524

Preparation of 3-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)-5-(4-trifluoromethoxyphenyl)-

3H-[1,3,4]oxadiazol-2-one

To a solution of 3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one prepared in Example 516 (3.27 g, 7.05 mmol) in 1,4-dioxane (70 ml), sodium hydride (0.37 g, 9.17 mmol) was added with cooling on ice-bath followed by stirring under reflux for 3 hours. The reaction mixture was concentrated under reduced pressure. To the solution, water was added with cooling on ice-bath, and the mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 4/1) and recrystallized from acetonitrile-ethanol to afford 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (1.43 g, yield 48%) as a white solid.

Melting point 190-191°C.

Using corresponding starting materials gave compounds of Examples 525 to 531 in the same manner as in Example 524.

Example 525

3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-trifluoromethylphenyl)-3H-[1,3,4]-oxadiazol-2-one

Melting point 230-231°C.

Example 526

3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(biphenyl-4-yl)-3H-[1,3,4]oxadiazol-2-one

Melting point 248-249°C.

Example 527

3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-chlorophenyl)-3H-[1,3,4]oxadiazol-2-one

Melting point 221-222°C.

Example 528

3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-fluorophenyl)-3H-[1,3,4]oxadiazol-2-one

Melting point 188-191°C.

Example 529

3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-[2-(4-chlorophenyl)vinyl]-3H-[1,3,4]-oxadiazol-2-one

Melting point 249-252°C.

Example 530

3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-[2-(4-chlorophenyl)ethyl]-3H-[1,3,4]-oxadiazol-2-one

Melting point 139-140°C.

Example 531

3-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-chlorophenoxymethyl)-3H-[1,3,4]-oxadiazol-2-one

Melting point 64-66°C.

Example 532

Preparation of 3-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)-5-phenyl-3H-[1,3,4]oxadiazol-2-one

A mixture of 2-chloro-4-nitro-1H-imidazole (170 mg, 1.15 mmol), 3-(2-methyloxiran-2-ylmethyl)-5-phenyl-3H-[1,3,4]oxadiazol-2-one (310 mg, 0.9 mmol), sodium hydrogencarbonate (120 mg, 1.43 mmol) and ethanol (2 ml) was stirred under reflux for 2.5 hours. The reaction mixture was allowed to return to room temperature, then diluted with water. The solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, the residue was dissolved in 1,4-dioxane (10 ml). To the solution, sodium hydride (55 mg, 1.38 mmol) was added followed by stirring at room temperature for 1 hour and then stirring under reflux for 1.5 hours. The reaction mixture was allowed to return to room temperature. To the solution, water was added, and the mixture was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from ethanol to afford 3-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)-5-phenyl-3H-[1,3,4]-oxadiazol-2-one (127 mg, yield 32%) as a light brown powder.

Melting point 225-227°C.

Example 533

Preparation of 5-(4-chlorobenzyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-[1,3,4]oxadiazol-2-one

A mixture of 2-methyloxiran-2-ylmethyl 4-methylbenzenesulfonate (3.98 g, 18.9 mmol), 5-(4-chlorobenzyl)-3H-[1,3,4]oxadiazol-2-one (5.5 g, 26.11 mmol), potassium carbonate (3.4 g, 24.6 mmol), sodium iodide (3.4 g, 22.68 mmol) and DMF (40 ml) was stirred at room temperature for 21 hours. To the reaction mixture, water was added, and the mixture was extracted with ethyl acetate twice. The organic phases were combined, washed with water three times, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure to afford a yellow oil (5.47 g).

A mixture of 2.3 g of the yellow oil (11.02 mmol), 2,4-dinitro-1H-imidazole (2.26 g, 14.3 mmol), sodium acetate (1.81 g, 22.07 mmol) and ethanol (22 ml) was stirred under reflux for 8 hours. The reaction mixture was allowed to return to room temperature. To the solution, water was added, and the mixture was extracted with ethyl acetate. The organic phase was washed with a saturated sodium hydrogencarbonate solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate

= 3/1) to afford 5-(4-chlorobenzyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-[1,3,4]oxadiazol-2-one (240 mg, 9%)as a white solid. Melting point 151-153°C.

Example 534

Preparation of 5-(4-bromophenyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-[1,3,4]-oxadiazol-2-one

A mixture of 2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl methanesulfonate prepared in Example 41 (1.02 g, 3.67 mmol), 5-(4-bromophenyl)-3H-[1,3,4]oxadiazol-2-one (680 mg, 2.82 mmol), potassium carbonate (580 mg, 4.2 mmol), sodium iodide (890 mg, 5.94 mmol) and DMF (15 ml) was stirred at 100°C for 3 hours. The reaction mixture was allowed to return to room temperature. To the solution, water was added, and the resulting solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water three times, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1) to afford 5-(4-bromophenyl)-3-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)-3H-[1,3,4]oxadiazol-2-one (17.4 mg, yield 2%) as a light yellow powder. Melting point 231-233°C.

Example 535

Preparation of 5-(4-bromophenyl)-3-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-[1,3,4]-oxadiazol-2-one

Using 6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl methanesulfonate prepared in Example 40 (3.28 g, 12.46 mmol) and 5-(4-bromophenyl)-3H-[1,3,4]oxadiazol-2-one (1.5 g, 6.22 mmol) gave 5-(4-bromophenyl)-3-(6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3H-[1,3,4]oxadiazol-2-one (312 mg, yield 12%) as a light brown powder in the same manner as in Example 534.

Melting point 264°C (decomposition).

Using corresponding starting materials gave the compound of Example 536 in the same manner as in Example 535.

Example 536

3-(6-Nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one

Melting point 204-207°C.

Example 537

Preparation of 3-[2-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-yl)ethyl]-5-(pyridin-4-yl)-3H-[1,3,4]oxadiazol-2-one

A mixture of 5-(pyridin-4-yl)-3H-[1,3,4]-oxadiazol-2-one (150 mg, 0.92 mmol), sodium hydride (41 mg, 1.03 mmol) and DMF (1.5 ml) was stirred at room temperature for 1 hour. To the reaction mixture, 2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

yl)ethyl methanesulfonate prepared in Example 42 (200 mg, 0.69 mmol) and sodium iodide (140 mg, 0.93 mmol) were added in this order followed by stirring at 50-60°C for 6 hours. The reaction mixture was allowed to return to room temperature. To the solution, water was added, and the resulting solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water three times, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 25/1) to afford 3-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-5-(pyridin-4-yl)-3H-[1,3,4]oxadiazol-2-one (137 mg, yield 56%) as a white powder.

Melting point 147-149°C.

Using corresponding starting materials gave the compound of Example 538 in the same manner as in Example 537.

Example 538

3-[2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-5-(pyrazin-2-yl)-3H-[1,3,4]oxadiazol-2-one

Melting point 209-212°C.

Example 539

Preparation of (R)-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one

To a solution of 5-(4-trifluoromethoxy-

phenyl)-3H-[1,3,4]oxadiazol-2-one (0.68 g, 2.76 mmol) and (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (0.50 g, 2.30 mmol) in DMF (5 ml), potassium carbonate (0.38 g, 2.76 mmol) was added followed by stirring at room temperature for 16 hours, and then water was added. The solution was extracted with ethyl acetate, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 4/1) to afford (R)-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (1.06 g, quantitative yield) as a white amorphous form.

^{1}H-NMR (DMSO-d_6) δppm:

1.53 (3H, s), 3.67 (1H, d, J = 8.8 Hz), 3.81 (1H, d, J = 8.8 Hz), 4.49 (2H, s), 7.42 - 7.66 (2H, m), 7.86 - 8.09 (2H, m), 8.54 (1H, s), 10.98 (1H, br).

Example 540

Preparation of (R)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one

To a solution of (R)-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one prepared in Example 539 (0.87 g, 1.88 mmol) in 1,4-dioxane (18 ml), sodium hydride (98 mg, 2.44 mmol) was added with cooling on ice-bath. The mixture was

stirred under reflux for 5 hours, concentrated under reduced pressure, then water was added with cooling on ice-bath. The solution was extracted with ethyl acetate, and the organic phase was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 9/1), and recrystallized from acetonitrile/isopropanol to afford (R)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-(4-trifluoromethoxyphenyl)-3H-[1,3,4]oxadiazol-2-one (0.32 g, yield 40%) as a white powder.

Optical purity 98.2% e.e.

$[\alpha]_D^{26}$ = -12.43° (concentration: 0.668, $CHCl_3$)

Melting point 146-148°C.

Example 541

Preparation of 3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3H-benzoxazol-2-one

To a suspension of 2-chloro-4-nitro-1H-imidazole (503 mg, 3.41 mmol), 3-(2-methyloxiran-2-yl-methyl)-3H-benzoxazol-2-one (700 mg, 3.41 mmol) in ethanol (7 ml), sodium acetate (336 mg, 4.1 mmol) was added followed by stirring under reflux for 8 hours. The reaction mixture was allowed to return to room temperature. To a mixture, water was added, and the resulting solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The filtrate was

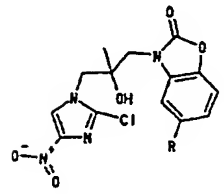
concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 30/1) to afford 3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3H-benzoxazol-2-one (616 mg, yield 51%) as a light yellow powder.

^{1}H-NMR ($CDCl_3$) δppm:

1.31 (3H, s), 3.04 (1H, s), 3.87 (1H, d, J = 14.7 Hz), 3.98 (1H, d, J = 14.7 Hz), 4.13 (1H, d, J = 12.5 Hz), 4.24 (1H, d, J = 14.5 Hz), 7.08 - 7.31 (4H, m), 8.04 (1H, s).

Using corresponding starting materials gave compounds of Examples 542 and 543 shown in the following table in the same manner as in Example 541.

Table 19



Example	R	^{1}H NMR δ		Yield (%)
542	Cl	$CDCl_3$	1.32(3H, s), 3.14(1H, s), 3.87(1H, d, J=14.7Hz), 3.95 (1H, d, J=14.7Hz), 4.11(1H, d, J=14.4Hz), 4.25(1H, d, J=14.4Hz), 7.10-7.23(3H, m), 8.03(1H, s).	35
543	F	$CDCl_3$	1.11(3H, s), 2.66(1H,s), 3.86(1H, d, J=14.5Hz), 3.94(1H, d, J=14.5Hz), 4.16(1H, d, J=14.3Hz), 4.24(1H, d, J=14.3Hz), 6.89-7.00(1H, m), 7.29 (1H, dd, J=2.7Hz, 8.8Hz), 7.37(1H, dd, J=4.4Hz, 8.8Hz), 8.01(1H,s).	33

Example 544

Preparation of 3-(2-methyl-6-nitro-2,3-dihydroimidazo-

[2,1-b]oxazol-2-ylmethyl)-3H-benzoxazol-2-one

A mixture of 3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3H-benzoxazol-2-one prepared in Example 541 (615 mg, 1.74 mmol), sodium hydride (76.6 mg, 1.91 mmol), 1,4-dioxane (15 ml) was stirred under reflux for 1 hour. The reaction mixture was allowed to return to room temperature. To the solution, water was added and the solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 30/1) to afford 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmetyl)-3H-benzoxazol-2-one (209 mg, yield 38%) as a white powder.

Melting point 222.7-224.3°C.

Using corresponding starting materials gave compounds of Examples 545 and 546 in the same manner as in Example 544.

Example 545

5-Chloro-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmetyl)-3H-benzoxazol-2-one

Melting point 207.6-207.9°C.

Example 546

5-Fluoro-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmetyl)-3H-benzoxazol-2-one

Melting point 246.2-246.8°C.

Example 547

Preparation of 5-bromo-3-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)-3H-benzoxazol-2-one

A mixture of 2-chloro-4-nitro-1H-imidazole (3.22 g, 21.8 mmol), 5-bromo-3-(2-methyloxiran-2-ylmethyl)-3H-benzoxazol-2-one (6.2 g, 21.8 mmol), sodium acetate (1.97 g, 24 mmol) and ethanol (50 ml) was stirred under reflux for 8 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, and the resulting solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was dissolved in 1,4-dioxane (60 ml). To the solution, sodium hydride (528 mg, 13.21 mmol) was added followed by stirring at 70-80°C for 17 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 30/1) to afford 5-bromo-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmetyl)-3H-benzoxazol-2-one (1.82 g, yield 37%) as a white powder.

Melting point 243-245.5°C.

Example 548

Preparation of 5-(2-chloro-4-nitroimidazol-1-ylmethyl)-3-(4-hydroxybiphenyl-3-yl)-5-methyloxazolidin-2-one

A mixture of 2-chloro-4-nitro-1H-imidazole (1.3 g, 8.78 mmol), 5-phenyl-3-(2-methyloxiran-2-yl-methyl)-3H-benzoxazol-2-one (2.47 g, 8.78 mmol), sodium acetate (792 mg, 9.66 mmol) and ethanol (30 ml) was stirred under reflux for 10 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, and the resulting solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to afford 5-(2-chloro-4-nitroimidazol-1-ylmethyl)-3-(4-hydroxybiphenyl-3-yl)-5-methyloxazolidin-2-one (1.82 g, yield 61%) as a white powder.

^{1}H-NMR (DMSO-d_6) δppm:

1.55 (3H, s), 3.85 (1H, d, J = 9.5 Hz), 3.98 (1H, d, J = 9.5 Hz), 4.46 (1H, d, J = 14.9 Hz), 4.56 (1H, d, J = 14.9 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.27 (1H, t, J = 7.3 Hz), 7.36 - 7.57 (6H, m), 8.52 (1H, s), 10.06 (1H, s).

Example 549

Preparation of 3-(2-methyl-6-nitro-2,3-dihydroimidazo-

[2,1-b]oxazol-2-ylmethyl)-5-phenyl-3H-benzoxazol-2-one

A mixture of 5-(2-chloro-4-nitroimidazol-1-ylmethyl)-3-(4-hydroxybiphenyl-3-yl)-5-methyloxazolidin-2-one prepared in Example 548 (1.23 g, 2.88 mmol), sodium hydride (127 mg, 3.16 mmol) and DMF (10 ml) was stirred at 100°C for 4 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with methylene chloride. The organic phase was washed with water and a saturated saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-phenyl-3H-benzoxazol-2-one (172 mg, yield 15%) as a yellowish brown powder.

Melting point 254-254.6°C.

Example 550

Preparation of 3-[2-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-yl)ethyl]-3H-benzoxazol-2-one

A mixture of 2-benzoxazolinone (240 mg, 1.8 mmol), sodium hydride (67 mg, 1.95 mmol) and DMF (10 ml) was stirred at room temperature for 30 minutes. To the reaction mixture, 2-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-yl)ethyl methanesulfonate prepared in Example 42 (500 mg, 1.7 mmol) was added

followed by stirring at 50-60°C for 4 hours. The reaction mixture was allowed to return to room temperature and poured into ice-water. The precipitates were filtered off and recrystallized from ethanol to afford 3-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-3H-benzoxazol-2-one (320 mg, yield 56%) as a light brown powder. Melting point 193-195°C.

Example 551

Preparation of 3-[5-(2-chloro-4-nitroimidazol-1-yl)-4-hydroxy-4-methylpentyl]-3H-benzoxazol-2-one

Using 3-[3-(2-methyloxiran-2-yl)propyl]-3H-benzoxazol-2-one (3.8 g, 16.3 mmol) gave 3-[5-(2-chloro-4-nitroimidazol-1-yl)-4-hydroxy-4-methylpentyl]-3H-benzoxazol-2-one (3.5 g, 68%) as a white powder in the same manner as in Example 541.

^{1}H-NMR ($CDCl_3$) δppm:

1.20 (3H, s), 1.49 - 1.70 (2H, m), 1.88 - 2.07 (2H, m), 2.68 (1H, s), 3.81 - 3.93 (2H, m), 4.00 (2H, s), 6.98 (1H, d, J = 7.3 Hz), 7.09 - 7.26 (3H, m), 8.00 (1H, s).

Example 552

Preparation of 3-[6-(2-chloro-4-nitroimidazol-1-yl)-5-hydroxy-5-methylhexyl]-3H-benzoxazol-2-one

Using 3-[4-(2-methyloxiran-2-yl)butyl]-3H-benzoxazol-2-one (1.2 g, 4.86 mmol) gave 3-[6-(2-chloro-4-nitroimidazol-1-yl)-5-hydroxy-5-methylhexyl]-3H-benzoxazol-2-one (1.2 g, 62%) as a white powder in the same manner as in Example 541.

^{1}H-NMR ($CDCl_3$) δppm:

1.16 (3H, s), 1.38 - 1.58 (4H, m), 1.67 - 1.86 (2H, m), 2.15 (1H, s), 3.87 (2H, t, J = 6.6 Hz), 3.98 (2H, s), 6.98 (1H, d, J = 7.8 Hz), 7.08 - 7.26 (3H, m), 8.01 (1H, s).

Example 553

Preparation of 3-[3-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-yl)propyl]-3H-benzoxazol-2-one

Using 3-[5-(2-chloro-4-nitroimidazol-1-yl)-4-hydroxy-4-methylpentyl]-3H-benzoxazol-2-one prepared in Example 551 (3.5 g, 9.2 mmol) gave 3-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl]-3H-benzoxazol-2-one (2.4 g, yield 76%) as a light yellow powder in the same manner as in Example 544.

Melting point 180-181°C.

Example 554

Preparation of 3-[4-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-yl)butyl]-3H-benzoxazol-2-one

Using 3-[6-(2-chloro-4-nitroimidazol-1-yl)-5-hydroxy-5-methylhexyl]-3H-benzoxazol-2-one prepared in Example 552 (1.2 g, 3 mmol) gave 3-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)butyl]-3H-benzoxazol-2-one (780 mg, yield 72%) as a light yellow powder in the same manner as in Example 544.

Melting point 155-158°C.

Example 555

Preparation of 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3-methyl-1,3-dihydro-

benzimidazol-2-one

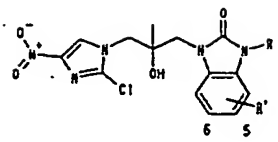
Using 1-methyl-3-(2-methyloxiran-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one (1.41 g, 6.46 mmol) gave 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3-methyl-1,3-dihydrobenzimidazol-2-one (1.23 g, yield 63%) as a white powder in the same manner as in Example 541.

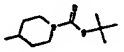
^{1}H-NMR ($CDCl_3$) δppm:

1.23 (3H, s), 3.47 (3H, s), 3.94 (1H, d, J = 12.4 Hz), 4.03 (1H, d, J = 12.4 Hz), 4.06 (1H, d, J = 11.9 Hz), 4.17 (1H, d, J = 11.9 Hz), 4.79 (1H, s), 7.00 - 7.21 (4H, m), 8.09 (1H, s).

Using corresponding starting materials gave compounds of Examples 556 to 565 shown in the following table in the same manner as in Example 555.

Table 20



Example	R	R'	^{1}H NMR δ	Yield (%)
556		H	1.23(3H, s), 1.51(9H, s), 1.75-1.89(2H, m), 2.17(2H, s), 2.20-2.41(2H, m), 2.75-2.91(2H, m), 3.90(1H, d, J=14.2Hz), 4.16(1H, d, J=14.2Hz), 4.25-4.50(3H, m), 7.00-7.23(4H, m), 8.09(1H, s).	78
557	Me	6-Cl	1.24(3H, s), 3.45(3H, s), 3.94(2H, s), 4.06(1H, d, J=14.4Hz), 4.18(1H, d, J=14.4Hz), 6.96(1H, d, J= 8.4Hz), 7.06(1H, d, J=1.9Hz), 7.16(1H, dd, J=1.9 Hz, 8.4 Hz), 8.08(1H, s)	69
558	Me	6-CF_3	1.26(3H, s), 3.51(3H, s), 3.95(1H, d, J=8.5Hz), 4.03 (1H, d, J=8.5Hz), 4.14(1H, d, J=14.3Hz), 4.21(1H, d, J=14.3Hz), 7.13(1H, d, J=8.3Hz), 7.31(1H, s), 7.48 (1H, d, J=8.3Hz), 8.07(1H, s).	61
559	Me	5-Cl	1.23(3H, s), 3.47(3H, s), 3.91(1H, d, J=14.8Hz), 3.99 (1H, d, J=14.8Hz), 4.05(1H, d, J =14.0Hz), 4.17(1H, d, J=14.0Hz), 6.97(1H, d, J=8.4Hz), 7.06(1H, d, J=1.9Hz), 7.14(1H, dd, J=1.9Hz, 8.4Hz), 8.07(1H, s).	56
560	Me	6-F	1.24(3H, s), 3.46(3H, s), 3.90(1H, d, J=14.8Hz), 3.97 (1H, d, J=14.8Hz), 4.06(1H, d, J=14.3Hz), 4.17(1H, d, J=14.3Hz), 6.79-7.00(3H, m), 8.08(1H, s).	63
561	Et	6-Cl	1.21(3H, s), 1.36(3H, t, J=7.2Hz), 3.84-4.20(6H, m), 6.98(1H, d, J=8.4Hz), 7.06(1H, d, J=1.8Hz), 7.15 (1H, dd, J=1.8Hz, 8.4Hz), 8.08(1H, s).	77
562	isopropyl	6-Cl	1.24(3H, s), 1.55(6H, d, J=7.0Hz), 3.93(2H, s), 4.06 (1H, d, J=14.3Hz), 4.17(1H, d, J=14.3Hz), 4.55-4.75 (1H, m), 7.05(1H, s), 7.18(2H, s), 8.09(1H, s).	69
563	Me	6-NMe_2	1.23(3H, s), 2.96(6H, s), 3.42(3H, s), 3.89(1H, d, J=14.8Hz), 3.99(1H, d, J=14.8 Hz), 4.05(1H, d, J= 14.3 Hz), 4.16(1H, d, J=14.3Hz), 6.39(1H, d, J= 2.2Hz), 6.60(1H, dd, J=2.2Hz, 8.6Hz), 6.92(1H, d, J =8.6Hz), 8.10(1H, s).	Crude
564	n-hexyl	6-Cl	0.87(3H, t, J=6.9Hz), 1.16-1.39(9H, m), 1.64 - 1.82 (2H, m), 3.80-3.93(4H, m), 4.05(1H, d, J=14.3Hz), 4.17(1H, d, J=14.3Hz), 6.97(1H, d, J=8.4Hz), 7.06 (1H, d, J=1.8Hz), 7.14(1H, dd, J=1.8Hz, 8.4Hz), 8.08 (1H, s).	55
565	Me	6-CO_2Et	1.25 (3H, s), 1.42 (3H, t, J=7.1Hz), 3.50 (3H, s), 3.93-4.11 (3H, m), 4.20 (1H, d, J=14.3Hz), 4.40 (2H, q. J=7.1Hz), 7.07 (1H, d, J=8.3Hz), 7.75 (1H, d, J= 1.5Hz), 7.94 (1H, dd, J=1.5Hz, 8.3Hz), 8.07 (1H, s).	48

Example 566

Preparation of 1-methyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one

Using 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3-methyl-1,3-dihydrobenzimidazol-2-one prepared in Example 555 (1.23 g, 3.37 mmol) gave 1-methyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one (563 mg, yield 51%) as a white powder in the same manner as in Example 544. Melting point 203.2-204.4°C.

Using corresponding starting materials gave compounds of Examples 567 to 576 in the same manner as in Example 566.

Example 567

1-(1-Tert-butoxycarbonylpiperidin-4-yl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one

Melting point 218-219.1°C.

Example 568

5-Chloro-1-methyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one

Melting point 261.9-265.4°C (decomposition).

Example 569

1-Methyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-5-trifluoromethyl-1,3-

dihydrobenzimidazol-2-one

Melting point 232.4-234.7°C.

Example 570

6-Chloro-1-methyl-3-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one

Melting point 261.3-263.3°C.

Example 571

5-Fluoro-1-methyl-3-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one

Melting point 244.2-249.8°C (decomposition).

Example 572

5-Chloro-1-ethyl-3-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one

Melting point 240.9-245.6°C.

Example 573

5-Chloro-1-isopropyl-3-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one

Melting point 240.5-244.8°C.

Example 574

5-Dimethylamino-1-methyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one

Melting point 264.6-268.3°C (decomposition).

Example 575

5-Chloro-1-(n-hexyl)-3-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one

Melting point 168.1-169.3°C.

Example 576

5-Ethoxycarbonyl-1-methyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one

Melting point 265.8-266.7°C.

Example 577

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)-3-phenyl-1,3-dihydro-benzimidazol-2-one

Using 1-(2-methyloxiran-2-ylmethyl)-3-phenyl-1,3-dihydrobenzimidazol-2-one (758 mg, 2.7 mmol) gave 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3-phenyl-1,3-dihydrobenzimidazol-2-one (70 mg, yield 13%) as a white powder in the same manner as in Example 200.

Melting point 234.5-234.7°C.

Using corresponding starting materials gave the compound of Example 578 in the same manner as in Example 577.

Example 578

1-(4-Fluorophenyl)-3-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydro-benzimidazol-2-one

Melting point 254.1-254.7°C.

Example 579

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)-(3-piperidin-4-yl)-1,3-dihydrobenzimidazol-2-one

A mixture of 1-(1-tert-butoxycarbonyl-piperidin-4-yl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)-1,3-dihydrobenzimidazol-2-one prepared in Example 567 (371 mg, 0.74 mmol), trifluoroacetic acid (1 ml) and methylene chloride (10 ml) was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. To the residue, a saturated sodium hydrogencarbonate solution, and the precipitates were filtered off. The precipitates were washed with water several times to afford 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-(3-piperidin-4-yl)-1,3-dihydrobenzimidazol-2-one (255 mg, yield 86%) as a light yellow powder.

Melting point 192.3-198.8°C (decomposition).

Example 580

Preparation of benzyl 4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-oxo-2,3-dihydrobenzimidazol-1-yl]piperidine-1-carboxylate

To a mixture of 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-(3-piperidin-4-yl)-1,3-dihydrobenzimidazol-2-one prepared in Example 579 (90 mg, 0.23 mmol) and methylene chloride (5 ml),

triethylamine (75 mg, 0.74 mmol) and benzyl chloroformate (126 mg, 0.74 mmol) were added in this order with cooling on ice-bath followed by stirring at room temperature for 3 hours. The reaction mixture was washed with water, a saturated sodium hydrogencarbonate solution and a saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/acetone = 1/1) to afford benzyl 4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2-oxo-2,3-dihydrobenzimidazol-1-yl]piperidine-1-carboxylate (25 mg, yield 21%) as a white powder.

Melting point 181.7-184.6°C.

Example 581

Preparation of 1-benzyl-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]imidazolidin-2-one

Using 1-benzyl-3-(2-methyloxiran-2-ylmethyl)-imidazolidin-2-one (680 mg, 2.76 mmol) gave 1-benzyl-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]imidazolidin-2-one (580 mg, yield 59%) as a white powder in the same manner as in Example 541.

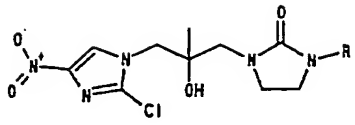
^{1}H-NMR ($CDCl_3$) δppm:

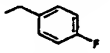
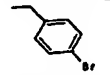
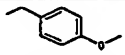
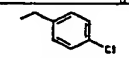
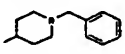
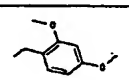
1.18 (3H, s), 3.17 - 3.54 (6H, m), 4.07 (2H, s), 4.37 (2H, s), 7.17 - 7.40 (5H, m), 8.13 (1H, s).

Using corresponding starting materials gave compounds of Examples 582 to 587 shown in the following

table in the same manner as in Example 581.

Table 21



Example	R (solvent)	^{1}H NMR δ	Yield (%)
582	 $CDCl_3$	1.19(3H, s), 3.16-3.52(6H, m), 4.06(2H, s), 4.33(2H, s), 6.93-7.09(2H, m), 7.18-7.30(2H, m), 8.13(1H, s).	43
583	 $CDCl_3$	1.19(3H, s), 3.16-3.55(6H, m), 4.05(2H, s), 4.31(2H, s), 7.14 (2H, dd, J=2.0Hz, 8.6Hz), 7.46(2H, dd, J=2.0Hz, 8.6 Hz), 8.13 (1H, s).	64
584	 DMSO-d_6	1.03(3H, s), 3.02-3.27(4H, m), 3.39-3.55(2H, m), 3.73(3H, s), 4.03(2H, s), 4.29(2H, s), 6.90(2H, d, J=8.6Hz), 7.17(2H, d, J=8.6Hz), 8.48(1H, s).	69
585	 DMSO-d_6	1.04(3H, s), 3.05-3.25(4H, m), 3.36-3.48(2H, m), 4.03(2H, s), 4.22(2H, s), 7.28(2H, d, J=8.3Hz), 7.41(2H, d, J=8.3Hz), 8.48(1H, s).	60
586	 $CDCl_3$	1.16(3H ,s), 1.59-1.84(4H, m), 2.00-2.18(2H, m), 2.89-3.02 (2H, m), 3.09-3.50(8H, m), 3.61-3.80(1H, m), 4.00(1H, d, J =14.3Hz), 4.09(1H, d, J=14.3Hz), 7.18-7.36(5H, m), 8.12 (1H, s).	Crude
587	 DMSO-d_6	1.03(3H, s), 3.05-3.23(4H, m), 3.30-3.50(2H, m), 3.75(3H, s), 3.77(3H, s), 4.02(2H, s), 4.20(2H, s), 6.47(1H, dd, J= 2.2Hz, 8.3Hz), 6.56(1H, d , J=2.2Hz), 7.06(1H, d, J=8.3Hz), 8.48 (1H, s).	58

Example 588

Preparation of 1-benzyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

Using 1-benzyl-3-[3-(2-chloro-4-nitro-imidazol-1-yl)-2-hydroxy-2-methylpropyl]imidazolidin-2-one prepared in Example 581 (580 mg, 1.47 mmol) gave 1-benzyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one (395 mg, yield

75%) as a white powder in the same manner as in Example 544.

Melting point 180.2-180.9°C.

Using corresponding starting materials gave compounds of Examples 589 to 594 in the same manner as in Example 588.

Example 589

1-(4-Fluorobenzyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

Melting point 182.5-183.3°C.

Example 590

1-(4-Bromobenzyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

Melting point 205.7-208.1°C.

Example 591

1-(4-Methoxybenzyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

Melting point 158.6-160.5°C.

Example 592

1-(4-Chlorobenzyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

Melting point 208.7-209.8°C.

Example 593

1-(1-Benzylpiperidin-4-yl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

^{1}H-NMR ($CDCl_3$) δppm:

1.41 - 1.72 (7H, m), 1.97 - 2.10 (2H, m), 2.88 - 2.95

(2H, m), 3.08 - 3.30 (4H, m), 3.43 - 3.70 (4H, m), 3.81 (1H, d, J = 15.0 Hz), 3.91 (1H, d, J = 10.3 Hz), 4.51 (1H, d, J = 10.3 Hz), 7.13 - 7.31 (5H, m), 7.47 (1H, s).

Example 594

1-(2,4-Dimethoxybenzyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

Melting point 175-175.4°C.

Example 595

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)-3-phenylimidazolidin-2-one

Using 1-(2-methyloxiran-2-ylmethyl)-3-phenylimidazolidin-2-one (300 mg, 1.29 mmol) gave 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-3-phenylimidazolidin-2-one (59 mg, yield 26%) as a white powder in the same manner as in Example 200.

Melting point 194.8-197.4°C.

Example 596

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one

A mixture of 1-(2,4-dimethoxybenzyl)-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one prepared in Example 594 (100 mg, 0.24 mmol), trifluoroacetic acid (2 ml) and methylene chloride (2 ml) was stirred at room temperature for 1 hour. To the reaction mixture, a saturated sodium hydrogencarbonate solution was added

for neutralization. The resulting solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was treated with diethyl ether to afford 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazolidin-2-one (50 mg, yield 78%) as a white powder.

Melting point 224.8-229.1°C (decomposition).

Example 597

Preparation of 3-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)oxazolidin-2-one

A mixture of 3-(2-methyloxiran-2-ylmethyl)-oxazolidin-2-one (2.87 g, 18.23 mmol), 2-chloro-4-nitro-1H-imidazole (2.7 g, 18.23 mmol), sodium acetate (1.64 g, 20.05 mmol) and ethanol (30 ml) was stirred under reflux for 10 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, methylene chloride was added, and the resulting solution was washed with water, a saturated sodium hydrogencarbonate solution and a saturated saline solution in this order, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was dissolved in 1,4-dioxane (50 ml). To the solution, sodium hydride (610 mg, 15.25 mmol) was added followed by stirring under reflux overnight. The reaction mixture was allowed to return to room

temperature and concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford 3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)oxazolidin-2-one (1.54 g, yield 40%) as a white powder.

^{1}H-NMR (DMSO-d_6) δppm:

1.59 (3H, s), 3.46 - 3.71 (4H, m), 4.11 - 4.30 (4H, m), 8.15 (1H, s).

Example 598

Preparation of 5-azidomethyl-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-oxazolidin-2-one

A mixture of 2-chloro-4-nitro-1H-imidazole (350 mg, 2.37 mmol), 5-azidomethyl-3-(2-methyloxiran-2-ylmethyl)oxazolidin-2-one (500 mg, 2.37 mmol), sodium acetate (214 mg, 2.61 mmol) and ethanol (5 ml) was stirred at 70°C for 8 hours. The reaction mixture was allowed to return to room temperature and concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue

was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/2) to afford 5-azidomethyl-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]oxazolidin-2-one (640 mg, yield 75%) as a light yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.23 (3H, s), 3.17 - 3.35 (2H, m), 3.43 - 3.61 (2H, m), 3.67 - 3.84 (2H, m), 4.01 - 4.16 (2H, m), 4.68 - 4.81 (1H, m), 8.04 (1H, s).

Example 599

Preparation of 5-azidomethyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)oxazolidin-2-one

5-Azidomethyl-3-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]oxazolidin-2-one prepared in Example 598 (1 g, 2.78 mmol) was dissolved in 1,4-dioxane (10 ml). To the solution, sodium hydride (130 mg, 3.25 mmol) was added followed by stirring at 80°C for 4 hours. The reaction mixture was allowed to return to room temperature and added water. The resulting solution was concentrated under reduced pressure. To the residue, water was added, and the solution was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 20/1) to afford 5-azidomethyl-3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)oxazolidin-

2-one (46 mg, yield 5%) as a light brown powder.

MS 323(M^+)

Example 600

Preparation of 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-1,4-dihydrobenzo[d][1,3]oxazin-2-one

Using 1-(2-methyloxiran-2-ylmethyl)-1,4-dihydrobenzo[d][1,3]oxazin-2-one (5.13 g, 23.04 mmol) gave 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-1,4-dihydrobenzo[d][1,3]oxazin-2-one (1.54 g, yield 36%) as a light yellow oil in the same manner as in Example 541.

^{1}H-NMR ($CDCl_3$) δppm:

1.23 (3H, s), 3.96 (1H, br), 4.04 - 4.20 (4H, m), 5.28 (2H, s), 7.00 - 7.07 (1H, m), 7.11 - 7.24 (2H, m), 7.30 - 7.43 (1H, m), 8.07 (1H, s).

Example 601

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)-1,4-dihydrobenzo[d][1,3]-oxazin-2-one

Using 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-1,4-dihydrobenzo[d][1,3]oxazin-2-one prepared in Example 600 (1.54 g, 4.20 mmol) gave 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one (0.58 g, yield 42%) as a light tan solid in the same manner as in Example 544.

Melting point 230-231°C.

Example 602

Preparation of 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3,3-difluoro-1,3-dihydroindol-2-one

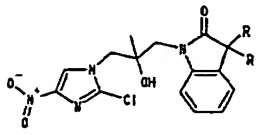
Using 3,3-difluoro-1-(2-methyloxiran-2-yl-methyl)-1,3-dihydroindol-2-one (1.14 g, 4.76 mmol) gave 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3,3-difluoro-1,3-dihydroindol-2-one (968 mg, yield 53%) as a white powder in the same manner as in Example 541.

^{1}H-NMR (DMSO-d_6) δppm:

1.09 (3H, s), 3.73 (1H, d, J = 14.5 Hz), 3.87 (1H, d, J = 14.5 Hz), 4.13 (1H, d, J = 14.4 Hz), 4.21 (1H, d, J = 14.4 Hz), 5.39 (1H, s), 7.20 - 7.26 (1H, m), 7.33 - 7.37 (1H, m), 7.57 - 7.64 (1H, m), 7.67 - 7.71. (1H, m).

Using corresponding starting materials gave compounds of Examples 603 and 604 shown in the following table in the same manner as in Example 602.

Table 22



Example	R	^{1}H NMR ($CDCl_3$) δ
603	Me	1.21(3H, s), 1.38(6H, s), 3.77(1H, d, J=14.8Hz), 3.87(1H, d, J=14.8Hz), 4.05 (1H, d, J=14.3Hz), 4.15(1H, d, J=14.3Hz), 6.91(1H, d, J=7.7Hz), 7.02-7.31 (3H, m), 8.07(1H, s).
604	H	1.24(3H, s), 3.64(2H, s), 3.79(1H, d, J=14.8Hz), 3.89(1H, d, J=14.8Hz), 4.09 (1H, d, J=14.3Hz), 4.19(1H, d, J=14.3Hz), 6.93(1H, d, J=7.7Hz), 7.12(1H, d, J=7.5Hz), 7.25-7.35(2H, m), 8.07(1H, s).

Example 605

Preparation of 3,3-difluoro-1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydroindol-2-one

Using 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-3,3-difluoro-1,3-dihydroindol-2-one prepared in Example 602 (903 mg, 2.34 mmol) gave 3,3-difluoro-1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,3-dihydroindol-2-one (77 mg, yield 9%) as a white powder in the same manner as in Example 544.

Melting point 202-206°C.

Using corresponding starting materials gave the compound of Example 606 in the same manner as in Example 605.

Example 606

3,3-Dimethyl-1-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)-1,3-dihydroindol-2-one

^{1}H-NMR (DMSO-d_6) δppm:

1.25 (3H, s), 1.37 (3H, s), 1.78 (3H, s), 3.96 (1H, d, J = 15.1 Hz), 4.00 (1H, d, J = 10.7 Hz), 4.22 (1H, d, J = 15.1 Hz), 4.57 (1H, d, J = 10.7 Hz), 7.04 - 7.17 (3H, m), 7.24 - 7.31 (1H, m), 7.44 (1H, s).

Example 607

Preparation of 1-(2-chloro-4-nitroimidazol-1-yl)-4-(1-ethyl-1H-tetrazol-5-yl)-2-methylbutan-2-ol

Using 1-ethyl-5-[2-(2-methyloxiran-2-yl)-ethyl]-1H-tetrazol (1.04 g, 5.59 mmol) gave 1-(2-

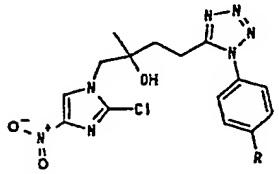
chloro-4-nitroimidazol-1-yl)-4-(1-ethyl-1H-tetrazol-5-yl)-2-methylbutan-2-ol (1.15 g, yield 69%) as a light yellow oil in the same manner as in Example 541.

^{1}H-NMR ($CDCl_3$) δppm:

1.29 (3H, s), 1.56 (3H, t, J = 7.3 Hz), 2.04 - 2.22 (2H, m), 2.91 - 3.11 (2H, m), 4.10 (2H, s), 4.24 (1H, br), 4.34 (2H, q, J = 7.3 Hz), 8.09 (1H, s).

Using corresponding starting materials gave compounds of Examples 608 and 609 shown in the following table in the same manner as in Example 607.

Table 23



Example	R	^{1}HNMR ($CDCl_3$) δ	Yield(%)
608	H	1.26(3H, s), 2.02-2.08(2H, m), 2.96-3.17(2H, m), 3.80(1H, s), 4.04(2H, s), 7.42-7.46(2H, m), 7.60-7.62(3H, m), 8.03(1H, s).	60
609	Cl	1.26(3H, s), 2.08-2.12(2H, m), 2.96-3.15(2H, m), 3.85(1H, s), 4.07(s,2H), 7.40-7.44(2H, m), 7.56-7.61(2H, m), 8.04(1H, s).	66

Example 610

Preparation of 2-[2-(1-ethyl-1H-tetrazol-5-yl)ethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Using 1-(2-chloro-4-nitroimidazol-1-yl)-4-(1-ethyl-1H-tetrazol-5-yl)-2-methylbutan-2-ol prepared in Example 607 (1.15 g, 3.49 mmol) gave 2-[2-(1-ethyl-1H-tetrazol-5-yl)ethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (68 mg, yield 7%) as a

light yellow powder in the same manner as in Example 544.

Melting point 135-137°C.

Using corresponding starting materials gave compounds of Examples 611 and 612 in the same manner as in Example 610.

Example 611

2-Methyl-6-nitro-2-[2-(1-phenyl-1H-tetrazol-5-yl)ethyl]-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 158-159°C.

Example 612

2-{2-[1-(4-Chlorophenyl)-1H-tetrazol-5-yl]ethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 198-200°C.

Example 613

Preparation of 3-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-5-(4-trifluoromethylbenzylidene)thiazolidine-2,4-dione

Using 2-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-yl)ethyl methanesulfonate prepared in Example 42 (280 mg, 0.96 mmol) and 5-(4-trifluoromethylbenzylidene)thiazolidine-2,4-dione (320 mg, 1.17 mmol) gave 3-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-5-(4-trifluoromethylbenzylidene)thiazolidine-2,4-dione (260 mg, yield 58%) as a light yellow powder in the same manner as in Example 537.

Melting point 257-258.5°C.

Example 614

Preparation of 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]pyrrolidine-2,5-dione

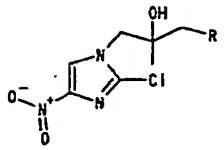
Using 1-(2-methyloxiran-2-ylmethyl)-pyrrolidine-2,5-dione (1.96 g, 11 mmol) gave 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]pyrrolidine-2,5-dione (589 mg, yield 16%) as a white powder in the same manner as in Example 541.

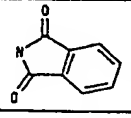
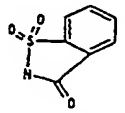
^{1}H-NMR (DMSO-d_6) δppm:

0.96 (3H, s), 2.68 (4H, s), 3.48 (2H, s), 4.02 (2H, s), 5.19 (1H, s), 8.34 (1H, s).

Using corresponding starting materials gave compounds of Examples 615 and 616 shown in the following table in the same manner as in Example 614.

Table 24



Example	R	^{1}H NMR δ ($CDCl_3$)	Yield (%)
615		1.21(3H, s), 3.48(1H, s), 3.79(1H, d, J=14.6Hz), 3.90(1H, d, J=14.6Hz), 4.01(1H, d, J=14.9Hz), 4.16(1H, d, J=14.9Hz), 7.75-7.93(4H, m), 8.06(1H, s).	71
616		1.21(3H, s), 4.09(1H, d, J=14.4Hz), 4.18(1H, d, J=14.4Hz), 4.05(1H, d, J=14.3Hz), 4.15(1H, d, J=14.3Hz), 4.42(1H, d, J=14.0Hz), 4.49(1H, d, J=14.0Hz), 7.60-7.74(2H, m), 7.81-8.12 (2H, m).	55

Example 617

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)pyrrolidine-2,5-dione

Using 1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]pyrrolidine-2,5-dione prepared in Example 614 (589 mg, 1.86 mmol) gave 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)pyrrolidine-2,5-dione (232 mg, yield 34%) as a white powder in the same manner as in Example 544.
Melting point 202.5-203.4°C.

Using corresponding starting materials gave compounds of Examples 618 and 619 in the same manner as in Example 617.

Example 618

2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)isoindole-1,3-dione
Melting point 264.6-268.3°C.

Example 619

2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,1-dioxo-1,2-dihydro[d]benzothiazol-3-one
Melting point 243-245°C (decomposition).

Example 620

Preparation of 1-(2-chloro-4-nitroimidazol-1-yl)-2-(pyridin-3-yl)-propan-2-ol

Using 3-(2-methyloxiran-2-yl)pyridine (7.4 g, 54.75 mmol) gave 1-(2-chloro-4-nitroimidazol-1-yl)-2-(pyridin-3-yl)propan-2-ol (3.3 g, yield 24%) as a white powder in the same manner as in Example 541.

^{1}H-NMR ($CDCl_3$) δppm:

1.65 (3H, s), 4.19 (1H, d, J = 14.2 Hz), 4.27 (1H, d, J = 14.2 Hz), 5.82 (1H, s), 7.24 - 7.30 (1H, m), 7.68 - 7.72 (1H, m), 8.50 - 8.53 (1H, m), 8.68 (1H, d, J = 2.3 Hz).

Example 621

Preparation of 2-methyl-6-nitro-2-(pyridin-3-yl)-2,3-dihydroimidazo[2,1-b]oxazole

Using 1-(2-chloro-4-nitroimidazol-1-yl)-2-(pyridin-3-yl)propan-2-ol prepared in Example 620 (3.3 g, 11.7 mmol) gave 2-methyl-6-nitro-2-(pyridin-3-yl)-2,3-dihydroimidazo[2,1-b]oxazole (1.8 g, yield 63%) as a light brown powder in the same manner as in Example 544.

Melting point 212-214°C.

Example 622

Preparation of 2-methyl-6-nitro-2-(1-oxypyridin-3-yl)-2,3-dihydroimidazo[2,1-b]oxazole

To a mixture of 2-methyl-6-nitro-2-(pyridin-3-yl)-2,3-dihydroimidazo[2,1-b]oxazole prepared in Example 621 (800 mg, 3.3 mmol) and methylene chloride (25 ml), m-chloroperbenzoic acid (1 g, 4.06 mmol) was added with cooling on ice-bath followed by stirring at room temperature overnight. The reaction mixture was filtered, and the filtrate was washed with a 20% aqueous sodium sulfite solution, a saturated sodium hydrogencarbonate solution and a saturated saline solution in this order, dried over magnesium sulfate

and then filtered. The filtrate was concentrated under reduced pressure to afford 2-methyl-6-nitro-2-(1-oxypyridin-3-yl)-2,3-dihydroimidazo[2,1-b]oxazole (330 mg, 39%) as a white powder.

^{1}H-NMR (DMSO-d_6) δppm:

1.92 (3H, s), 4.51 (2H, s), 7.42 - 7.53 (2H, m), 8.14 (1H, s), 8.20 - 8.24 (1H, m), 8.42 (1H, s).

Example 623

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)pieridin-4-one

Using 1-(2-methyloxiran-2-ylmethyl)piperidin-4-one (2.2 g, 13 mmol) gave 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-one (50 mg, yield 1%) as a light yellow powder in the same manner as in Example 597.

Melting point 124-126°C.

Example 624

Preparation of 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-1-(4-trifluoromethylbenzyl)-piperazin-2-one

Using 4-(2-methyloxiran-2-ylmethyl)-1-(4-trifluoromethylbenzyl)piperazin-2-one (1.6 g, 4.9 mmol) gave 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-1-(4-trifluoromethylbenzyl)piperazin-2-one (1 g, yield 43%) as a light yellow powder in the same manner as in Example 541.

^{1}H-NMR ($CDCl_3$) δppm:

1.18 (3H, s), 2.45 (1H, d, J = 13.9 Hz), 2.57 (1H, d, J

= 13.9 Hz), 2.72 - 2.98 (2H, m), 3.19 - 3.44 (3H, m), 3.55 (1H, d, J = 16.5 Hz), 4.00 (1H, d, J = 14.3 Hz), 4.10 (1H, d, J = 14.3 Hz), 4.64 (2H, s), 7.37 (2H, d, J = 8.2 Hz), 7.61 (2H, d, J = 8.2 Hz), 8.02 (1H, s).

Using corresponding starting materials gave the compound of Example 625 in the same manner as in Example 624.

Example 625

1-Tert-butyl-4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-2-one

^{1}H-NMR ($CDCl_3$) δppm:

1.16 (3H, s), 1.44 (9H, s), 2.41 (1H, d, J = 13.8 Hz), 2.51 (1H, d, J = 13.8 Hz), 2.65 - 2.88 (3H, m), 2.93 - 3.09 (1H, m), 3.12 - 3.28 (2H, m), 3.99 (1H, d, J = 14.3 Hz), 4.08 (1H, d, J = 14.3 Hz), 8.05 (1H, s).

Example 626

Preparation of 4-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)-1-(4-trifluoromethylbenzyl)-piperazin-2-one

Using 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]-1-(4-trifluoromethylbenzyl)-piperazin-2-one prepared in Example 624 (1 g, 2.1 mmol) gave 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1-(4-trifluoromethylbenzyl)piperazin-2-one (206 mg, yield 22%) as a light yellow powder in the same manner as in Example 544.

Melting point 88-93°C.

Using corresponding starting materials gave the compound of Example 627 in the same manner as in Example 626.

Example 627

1-Tert-butyl-4-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)piperazin-2-one

Melting point 193-194°C.

Example 628

Preparation of 1-tert-butyl-4-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]piperazin-2-one

A mixture of 2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl methanesulfonate prepared in Example 42 (290 mg, 1 mmol), 1-tert-butylpiperazin-2-one hydrochloride (200 mg, 1.28 mmol), triethylamine (242 mg, 2.39 mmol), potassium iodide (250 mg, 1.5 mmol) and DMF (3 ml) was stirred at 70°C for 4 hours. The reaction mixture was allowed to return to room temperature. To the solution, water was added, and the resulting solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water twice and a saturated saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to afford 1-tert-butyl-4-[2-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]piperazin-2-one (27 mg, yield 8%) as a white powder.

Melting point 153-154°C.

Using corresponding starting materials gave the compound of Example 629 in the same manner as in Example 628.

Example 629

4-[2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)ethyl]-1-phenylpiperazin-2-one

Melting point 199-202°C (decomposition).

Example 630

Preparation of 1-tert-butyl-4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl]piperazin-2-one

Using 3-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-yl)propyl methanesulfonate prepared in Example 39 (300 mg, 0.98 mmol) gave 1-tert-butyl-4-[3-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-yl)propyl]piperazin-2-one (150 mg, yield 42%) as a white powder in the same manner as in Example 628.

Melting point 147-149°C (decomposition).

Example 631

Preparation of 1-(benzimidazol-1-yl)-3-(2-chloro-4-nitroimidazol-1-yl)-2-methylpropan-2-ol

Using 1-(2-methyloxiran-2-ylmethyl)-1H-benzimidazole (350 mg, 1.86 mmol) gave 1-(benzimidazol-1-yl)-3-(2-chloro-4-nitroimidazol-1-yl)-2-methylpropan-2-ol (135 mg, yield 22%) as a white powder in the same manner as in Example 541.

^{1}H-NMR (DMSO-d_6) δppm:

0.99 (3H, s), 4.06 (1H, d, J = 14.2 Hz), 4.23 - 4.45

(3H, m), 5.44 (1H, s), 7.14 - 7.32 (2H, m), 7.57 - 7.77 (2H, m), 8.15 (1H, s), 8.36 (1H, s).

Using corresponding starting materials gave the compound of Example 632 in the same manner as in Example 631.

Example 632

1-(Imidazol-1-yl)-3-(2-chloro-4-nitroimidazol-1-yl)-2-methylpropan-2-ol

^{1}H-NMR ($CDCl_3$) δppm:

1.19 (3H, s), 3.86 - 4.05 (3H, m), 4.13 (1H, d, J = 14.2 Hz), 6.87 (1H, s), 6.89 (1H, s), 7.47 (1H, s), 8.08 (1H, s).

Example 633

Preparation of 1-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)-1H-benzimidazole

Using 1-(benzimidazol-1-yl)-3-(2-chloro-4-nitroimidazol-1-yl)-2-methylpropan-2-ol prepared in Example 631 (135 mg, 0.4 mmol) gave 1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1H-benzimidazole (72 mg, yield 60%) as a white powder in the same manner as in Example 544.

Melting point 250.3-251.9°C (decomposition).

Using corresponding starting materials gave the compound of Example 634 in the same manner as in Example 633.

Example 634

1-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)imidazole

Melting point 245.5-247.8°C.

Example 635

Preparation of (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-(3,4-dihydro-2H-quinolin-1-yl)-2-methylpropan-2-ol

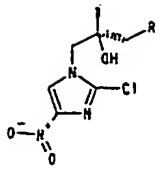
A mixture of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (100 mg, 0.46 mmol), 1,2,3,4-tetrahydroquinoline (122 mg, 0.92 mmol) and DMF (1 ml) was stirred at 80°C for 8 hours. The reaction mixture was allowed to return to room temperature. To the solution, water was added, and the resulting solution was extracted with ethyl acetate twice. The organic phases were combined, washed with water twice and a saturated saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1) to afford (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-(3,4-dihydro-2H-quinolin-1-yl)-2-methylpropan-2-ol (134 mg, yield 83%) as an orange oil.

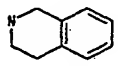
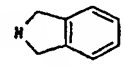
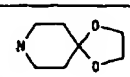
^{1}H-NMR ($CDCl_3$) δppm:

1.24 (3H, s), 1.94 - 2.04 (2H, m), 2.39 (1H, m), 2.79 - 2.85 (2H, m), 3.27 - 3.42 (4H, m), 6.66 - 6.72 (2H, m), 6.97 - 7.08 (2H, m), 8.04 (1H, s).

Using corresponding starting materials gave compounds of Examples 636 to 638 shown in the following table in the same manner as in Example 635.

Table 25



Example	R	^{1}H NMR δ ($CDCl_3$)	Yield (%)
636		1.18(3H, s), 2.51(1H, d, J=13.9Hz), 2.66(1H, d, J=13.9Hz), 2.82-2.98(4H, m), 3.76(1H, d, J=14.9Hz), 3.88(1H, d, J=14.9Hz), 4.03(2H, s), 7.00(1H, dd, J=2.3Hz, 7.7Hz), 7.06-7.20 (3H, m), 8.01(1H, s).	87
637		1.20(3H, s), 2.55(1H, d, J=13.8Hz), 2.71(1H, d, J = 13.8Hz), 3.81(1H, d, J=14.8Hz), 3.91(1H, d, J=14.8Hz), 4.05(4H, s), 7.10-7.23(4H, m), 8.00(1H, s).	93
638		1.11(3H, s), 1.67-1.78(4H, m), 2.37(1H, d, J=14.0Hz), 2.51 (1H, d, J=14.0Hz), 2.57-2.82(4H, m), 3.69(1H, s), 3.95(4H, s), 3.99(2H, s), 8.06(1H, s).	100

Example 639

Preparation of (S)-1-(2-methyl-6-nitro-2,3-dihydro-imidazo[2,1-b]oxazol-2-ylmethyl)-1,2,3,4-tetrahydro-quinoline

Using (S)-1-(2-chloro-4-nitroimidazol-1-yl)-3-(3,4-dihydro-2H-quinolin-1-yl)-2-methylpropan-2-ol prepared in Example 635 (134 mg, 0.38 mmol) gave (S)-1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,2,3,4-tetrahydroquinoline (64 mg, 54%) as a white powder in the same manner as in Example 393. Melting point 168-172°C.

Using corresponding starting materials gave compounds of Examples 640 to 642 in the same manner as in Example 639.

Example 640

(S)-2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-

b]oxazol-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline

Melting point 153-155.3°C.

Example 641

(S)-2-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-2,3-dihydro-1H-isoindole

^{1}H-NMR ($CDCl_3$) δppm:

1.68 (3H, s), 3.01 (1H, d, J = 14.5 Hz), 3.24 (1H, d, J = 14.5 Hz), 3.92 (1H, d, J = 9.6 Hz), 4.08 (4H, s), 4.50 (1H, d, J = 9.6 Hz), 7.13 - 7.21 (4H, m), 7.50 (1H, s).

Example 642

(S)-8-(2-Methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-1,4-dioxa-8-azaspiro[4,5]decane

Melting point 166.5-168.2°C.

Example 643

Preparation of (2S)-methyl-6-nitro-2-[(2S)-(4-trifluoromethoxyphenoxymethyl)pyrrolidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of (R)-2-chloro-1-(2-methyloxiran-2-ylmethyl)-4-nitroimidazole prepared in Example 12 (645 mg, 2.97 mmol), (S)-2-(4-trifluoromethoxyphenoxymethyl)pyrrolidine (930 mg, 3.56 mmol) and DMF (15 ml) was stirred at 80°C for 8 hours. To the reaction mixture, sodium hydride (154 mg, 3.86 mmol) was added followed by stirring for 1 hour with cooling on ice-bath. The reaction mixture was poured into ice-water, and the mixture was extracted with ethyl acetate twice. The organic phases were combined, washed with water

twice and a saturated saline solution, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride) and recrystallized from methylene chloride-isopropyl ether to afford (2S)-methyl-6-nitro-2-[(2S)-(4-trifluoromethoxyphenoxymethyl)pyrrolidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole (505 mg, yield 41%) as a white powder.

^{1}H-NMR ($CDCl_3$) δppm:

1.42 - 1.52 (1H, m), 1.59 (3H, s), 1.61 - 1.79 (2H, m), 1.87 - 1.99 (1H, m), 2.50 - 2.61 (1H, m), 3.03 - 3.17 (2H, m), 3.06 (1H, d, J = 14.7 Hz), 3.20 (1H, d, J = 14.7 Hz), 3.72 - 3.79 (2H, m), 3.92 (1H, dd, J = 9.2 Hz, 3.7 Hz), 4.58 (1H, d, J = 9.5 Hz), 6.80 - 6.88 (2H, m), 7.15 - 7.19 (1H, m), 7.42 (1H, s).

Example 644

Preparation of tert-butyl 4-[3-(2-chloro-4-nitro-imidazol-1-yl)-2-hydroxy-2-methylpropyl]homopiperazine-1-carboxylate

A mixture of 2-chloro-4-nitro-1H-imidazole (8.39 g, 56.88 mmol), tert-butyl 4-(2-methyloxiran-2-ylmethyl)homopiperazine-1-carboxylate (15.38 g, 56.88 mmol) and sodium acetate (5.13 g, 62.57 mmol) in 1-propanol (100 ml) was stirred under reflux for 10 hours. The reaction mixture was allowed to return to room temperature and then concentrated under reduced pressure. The residue was dissolved in methylene

chloride. The solution was washed with water, dried over sodium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 5/1) to afford tert-butyl 4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]homopiperazine-1-carboxylate (6.25 g, yield 27%) as a reddish yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.14 (3H, s), 1.48 (9H, s), 1.69 - 1.90 (2H, m), 2.40 - 2.55 (1H, m), 2.66 (1H, d, J = 14.1 Hz), 2.75 - 2.98 (5H, m), 3.30 - 3.59 (4H, m), 3.96 (2H, s), 8.06 (1H, s).

Example 645

Preparation of tert-butyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)homopiperazin-1-carboxylate

Using tert-butyl 4-[3-(2-chloro-4-nitro-imidazol-1-yl)-2-hydroxy-2-methylpropyl]homopiperazine-1-carboxylate prepared in Example 644 (6.25 g, 14.96 mmol) gave tert-butyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)homopiperazine-1-carboxylate (3.07 g, yield 54%) as a white powder in the same manner as in Example 544.

^{1}H-NMR ($CDCl_3$) δppm:

1.47 (9H, s), 1.59 (3H, s), 1.68 - 1.79 (2H, m), 2.63 - 2.90 (5H, m), 3.06 (1H, d, J = 15.1 Hz), 3.25 - 3.50

(4H, m), 3.91 (1H, d, J = 9.7 Hz), 4.33 (1H, d, J = 9.7 Hz), 7.54 (1H, s).

Example 646

Preparation of benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)homopiperazine-1-carboxylate hydrochloride

A mixture of tert-butyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-homopiperazine-1-carboxylate prepared in Example 645 (250 mg, 0.655 mmol) and trifluoroacetic acid (10 ml) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in methylene chloride (10 ml). To the solution, triethylamine (0.27 ml, 1.96 mmol) and benzyl chloroformate (0.19 ml, 1.31 mmol) were added followed by stirring at room temperature for 3 hours. To the reaction mixture, water was added, and the mixture was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 1/1) to afford a light yellow oil. The resulting oil was dissolved in ethyl acetate. To the solution, a saturated hydrochloric acid/ethyl acetate solution was added, and the precipitates were filtered off to afford benzyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

ylmethyl)homopiperazine-1-carboxylate hydrochloride (246 mg, yield 83%) as a white powder.

Melting point 115-117°C.

Example 647

Preparation of 2-[4-(biphenyl-4-ylmethyl)homopiperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

A mixture of tert-butyl 4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-homopiperazin-1-carboxylate prepared in Example 645 (346 mg, 0.91 mmol) and trifluoroacetic acid (10 ml) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride (10 ml). To the solution, triethylamine (0.27 ml, 1.96 mmol) was added. The solution was concentrated under reduced pressure, and the residue was dissolved in methanol (10 ml). To the solution, 4-phenylbenzaldehyde (496 mg, 2.72 mmol), sodium cyanotrihydroborate (171 mg, 2.72 mmol) and acetic acid (0.17 ml, 2.72 mmol) were added in this order followed by stirring at room temperature overnight. The reaction mixture was poured into a saturated sodium hydrogencarbonate solution, then extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography

(methylene chloride/ethyl acetate = 5/1) to afford 2-[4-(biphenyl-4-ylmethyl)homopiperazin-1-ylmethyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole (251 mg, yield 62%) as a white powder.

Melting point 138-142.2°C.

Example 648

Preparation of 1'-tert-butoxycarbonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazol-2,4'-piperidine]

2,4-Dinitro-1H-imidazole (1.0 g, 6.3 mmol), tert-butyl 1-oxa-6-azaspiro[2,5]octane-6-carboxylate (2.0 g, 9.5 mmol) and sodium acetate (612 mg, 7.5 mmol) in ethanol (7 ml) were stirred under reflux for 10 hours. The reaction mixture was concentrated under reduced pressure. To the residue, a saturated sodium hydrogencarbonate solution and methylene chloride were added followed by stirring vigorously, and then the mixture was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure, and the residue was crystallized from methylene chloride-diisopropyl ether to afford 1'-tert-butoxycarbonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (586 mg, yield 29%) as a white powder.

Melting point 230-232°C.

Example 649

Preparation of tert-butyl 4-(2-chloro-4-nitroimidazol-1-ylmethyl)-4-hydroxypiperidine-1-carboxylate

2-Chloro-4-nitro-1H-imidazole (3.1 g, 21.0 mmol), tert-butyl 1-oxa-6-azaspiro[2,5]octane-6-carboxylate (4.4 g, 21.0 mmol) and sodium hydrogencarbonate (1.94 g, 23.1 mmol) in ethanol (20 ml) were stirred under reflux for 6 hours. The reaction mixture was concentrated under reduced pressure, and the residue was added water. The resulting solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford tert-butyl 4-(2-chloro-4-nitroimidazol-1-ylmethyl)-4-hydroxypiperidine-1-carboxylate (5.4 g, yield 72%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.45 - 1.71 (5H, m), 1.46 (9H, s), 3.03 - 3.14 (2H, m), 3.90 - 4.03 (2H, m), 4.02 (2H, s), 7.91 (1H, s).

Example 650

Preparation of tert-butyl 4-{2-[4-(2-chloro-4-nitroimidazol-1-ylmethyl)-4-hydroxypiperidin-1-yl]-2-oxoethyl}piperazine-1-carboxylate

2-Chloro-4-nitro-1H-imidazole (1.29 g, 8.76 mmol), tert-butyl 4-{2-(1-oxa-6-azaspiro[2,5]octan-6-yl)-2-oxoethyl}piperazine-1-carboxylate (2.97 g, 8.76 mmol) and sodium hydrogencarbonate (809 mg, 9.64 mmol) in ethanol (10 ml) was stirred under reflux for 5 hours. The reaction mixture was concentrated under

reduced pressure, and a saturated sodium hydrogencarbonate solution was added. The solution was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) to afford tert-butyl 4-{2-[4-(2-chloro-4-nitroimidazol-1-ylmethyl)-4-hydroxypiperidin-1-yl]-2-oxoethyl}piperazine-1-carboxylate (2.58 g, yield 61%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δppm:

1.45 (9H, s), 1.53 - 1.71 (4H, m), 2.44 (4H, br), 2.96 - 3.04 (1H, m), 3.10 - 3.27 (2H, m), 3.35 - 3.48 (4H, m), 3.90 - 3.96 (2H, m), 4.05 (2H, s), 4.32 - 4.37 (2H, m), 8.04 (1H, s).

Using 6-(4-trifluoromethylphenyl)-1-oxa-6-azaspiro[2,5]octane gave the compound of Example 651 in the same manner as in Example 650.

Example 651

4-(2-Chloro-4-nitroimidazol-1-ylmethyl)-1-(4-trifluoromethylphenyl)piperidin-4-ol

Light pink powder, yield 54%

^{1}H-NMR ($CDCl_3$) δppm:

1.60 - 1.66 (2H, m), 1.82 - 1.93 (3H, m), 3.10 - 3.22 (2H, m), 3.62 - 3.67 (2H, m), 4.07 (2H, s), 6.95 (2H, d, J = 8.7 Hz), 7.50 (2H, d, J = 8.7 Hz), 7.99 (1H, s).

Example 652

Preparation of 1'-tert-butoxycarbonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-(alternative synthesis method of the compound of Example 648)

Tert-butyl 4-(2-chloro-4-nitroimidazol-1-ylmethyl)-4-hydroxypiperidine-1-carboxylate prepared in Example 649 (26.7 g, 74.0 mmol) was dissolved in 1,4-dioxane (200 ml). To the solution, sodium hydride (3.6 g, 88.8 mmol) was added with cooling on ice-bath followed by stirring under reflux for 8 hours. The reaction mixture was concentrated under reduced pressure. To the residue, ice-water and methylene chloride were added followed by stirring vigorously. The precipitates were filtered off, washed with water and methanol, dried under reduced pressure to afford a solid (16.4 g). Then, the filtrate was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The organic phase was concentrated under reduced pressure. The residue was crystallized with methanol to afford a solid (2.7 g). The solids were combined to afford 1'-tert-butoxycarbonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (19.1 g, yield 79%) as a white powder.

Melting point 230-232°C.

Example 653

Preparation of tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazol-2,4'-piperidine]-1'-

yl)-2-oxoethyl]piperazine-1-carboxylate

Tert-butyl 4-{2-[4-(2-chloro-4-nitroimidazol-1-ylmethyl)-4-hydroxypiperidin-1-yl]-2-oxoethyl}-piperazine carboxylate prepared in Example 650 (2.58 g, 5.3 mmol) was dissolved in dioxane (30 ml). To the solution, sodium hydride (254 mg, 6.36 mmol) was added with cooling on ice-bath followed by stirring under reflux overnight. The reaction mixture was concentrated under reduced pressure. To the residue, ice-water and ethyl acetate were added followed by stirring vigorously. The precipitates were filtered off, washed with water and ethyl acetate, and then dried under reduced pressure to afford tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazol-2,4'-piperidine]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate (996 mg, yield 42%) as a white powder.

Melting point 211.0-213.0°C.

Using corresponding starting materials gave the compound of Example 654 in the same manner as in Example 653.

Example 654

2,3-Dihydro-6-nitro-1'-(4-trifluoromethylphenyl)spiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

White powder, yield 79%

MS: 368(M^+)

Melting point 249.2-250.1°C.

Example 655

Preparation of 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate

1'-Tert-butoxycarbonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] prepared in Example 652 (42 g, 0.13 mol) was suspended in methylene chloride (100 ml). To the suspension, trifluoroacetic acid (60 ml) was added slowly with cooling on ice-bath followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized with methanol. The solids were filtered off, washed with methanol and ethyl acetate, and then dried under reduced pressure to afford 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate (43.6 g, yield 99%) as a light brown powder.

MS: 224(M^+)

Melting point 196-198°C (decomposition)

^{1}H-NMR (DMSO-d_6) δppm:

2.06 - 2.32 (4H, m), 3.12 - 3.35 (4H, m), 4.24 (2H, s), 8.21 (1H, s), 8.88 (2H, bs).

Example 656

Preparation of 1'-acetyl-2,3-dihydro-6-nitrospiro-[imidazo[2,1-b]oxazole-2,4'-piperidine]

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (85.5 mg, 0.25 mmol) was suspended in methylene chloride (5 ml). To the suspension,

triethylamine (74 μl) and acethyl chloride (20 μl) were added followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. To the residue, methanol and water were added followed by stirring vigorously. The precipitates were filtered off, washed with water and isopropyl ether, and then dried under reduced pressure to afford 1'-acetyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (37.8 mg, yield 56%) as a white powder.

MS: 266(M^+)

Melting point 232.0-234.0°C.

Example 657

Preparation of 1'-(4-trifluoromethylphenylacetyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (300 mg, 0.89 mmol) was suspended in methylene chloride (5 ml). To the suspension, triethylamine (0.4 ml, 2.66 mmol) and (α,α,α-trifluoro-p-tolyl)acetyl chloride (2.7 ml, 1.33 mmol) were added followed by stirring at room temperature for 1 hour. The reaction mixture was poured into a saturated sodium hydrogencarbonate solution, and the mixture was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced

pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford 1'-(4-trifluoromethyl-phenylacetyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (143 mg, yield 39%) as a white powder.

MS: 410(M^+)

Melting point 185.0-187.0°C.

Example 658

Preparation of 1'-(3,4-dichlorophenoxyacetyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (300 mg, 0.89 mmol), (3,4-dichlorophenyl)-acetic acid (294 mg, 1.24 mmol) and WSCD (255 mg, 1.24 mmol) in DMF (5 ml) were stirred at room temperature for 1.5 hours. To the reaction mixture, water and diethyl ether was added followed by stirring vigorously. The precipitates were filtered off, washed with water and diethyl ether, and then dried under reduced pressure to afford 1'-(3,4-dichlorophenoxy-acetyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (96 mg, yield 25%) as a white powder.

Melting point 218.0-220.0°C.

Example 659

Preparation of 2,3-dihydro-1'-methyl-6-nitrospiro-

[imidazo[2,1-b]oxazole-2,4'-piperidine]

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (250 mg, 1.12 mmol) obtained by neutrlization of 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 was suspended in methanol (5 ml). To the suspension, a 37% formaldehyde solution (0.25 ml, 3.35 mmol), sodium cyanotrihydroborate (210 mg, 3.35 mmol) and acetic acid (0.19 ml, 3.35 mmol) were added followed by stirring at room temperature for 3 hours. The reaction mixture was poured into a saturated sodium hydrogencarbonate solution, and the mixture was extracted with methylene chloride. The organic phase was dried over sodium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was crystallized from methylene chloride-diisopropyl ether to afford 2,3-dihydro-1'-methyl-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (160 mg, yield 60%) as a white powder.

MS: 238(M^+)

Melting point 237.0-239.0°C (decomposition).

Example 660

Preparation of 1'-benzenesulfonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (197 mg, 0.88 mmol) was suspended in

methylene chloride (5 ml). To the suspension, triethylamine (0.36 ml, 2.64 mmol) and benzenesulfonyl chloride (0.28 ml, 2.10 mmol) were added followed by stirring at room temperature for 30 minutes. To the reaction mixture, diisopropyl ether and water were added followed by stirring vigorously. The precipitates were filtered off, washed with water and diisopropyl ether, and then dried under reduced pressure to afford 1'-benzenesulfonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (210 mg, yield 66%) as a white powder.

MS: 364(M^+)

^{1}H-NMR (DMSO-d_6) δppm:

1.99 - 2.18 (4H, m), 2.49 - 2.63 (2H, m), 3.40 - 3.54 (2H, m), 4.10 (2H, s), 7.65 - 7.81 (5H, m), 8.21 (1H, s).

Using corresponding starting materials gave the compound of Example 661 in the same manner as in Example 660.

Example 661

1'-Methanesulfonyl-2,3-dihydro-6-nitrospiro[imidazo-[2,1-b]oxazole-2,4'-piperidine]

^{1}H-NMR (DMSO-d_6) δppm:

1.98 - 2.22 (4H, m), 2.94 (3H, s), 3.04 - 3.13 (2H, m), 3.43 - 3.51 (2H, m), 4.16 (2H, s), 8.17 (1H, s).

Example 662

Preparation of 1'-benzyloxycarbonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (250 mg, 0.74 mmol) was suspended in methylene chloride (5 ml). To the suspension, triethylamine (0.40 ml, 2.96 mmol) and benzyl chloroformate (0.32 ml, 2.22 mmol) were added followed by stirring at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford 1'-benzyloxycarbonyl-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (224 mg, yield 84%) as a white powder. Melting point 175.0-177.0°C.

Example 663

Preparation of 1'-(4-trifluoromethylbenzyloxycarbonyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (33 g, 97.6 mmol) was suspended in DMF (200 ml). To the suspension, triethylamine (20 ml, 0.15 mol) was added followed by stirring. To the solution, a mixture of 4-trifluoromethylbenzyl alcohol (25.8 g, 0.15 mol), 1,1'-carbonyldiimidazole (23.7 g, 0.15 mol) and DMF (100 ml) stirred at room temperature for 3 hours was added followed by stirring at 70°C for 2

hours. The reaction mixture was concentrated under reduced pressure. To the residue, water was added, and the precipitates were filtered off. The precipitates were purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/1) and recrystallized from ethyl acetate-isopropyl ether to afford 1'-(4-trifluoromethylbenzyloxycarbonyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] (37.2 g, yield 90%) as a white powder. Melting point 189-190°C.

Using corresponding starting materials gave compounds of Examples 664 and 665 in the same manner as in Example 663.

Example 664

1'-[(4-Trifluoromethoxy)benzyloxycarbonyl]-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

^{1}H-NMR ($CDCl_3$) δppm:

1.80 - 1.93 (2H, m), 2.13 - 2.19 (2H, m), 3.32 - 3.42 (2H, m), 4.00 - 4.20 (2H, m), 4.03 (2H, s), 5.14 (2H, s), 7.20 - 7.23 (2H, m), 7.38 - 7.46 (2H, m), 7.54 (1H, s).

Example 665

1'-(4-Formylaminobenzyloxycarbonyl)-2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]

^{1}H-NMR (DMSO-d_6) δppm:

1.85 - 2.10 (4H, m), 3.15 - 3.40 (2H, m), 3.65 - 3.85 (2H, m), 4.16 (2H, s), 5.03 (2H, s), 7.33 (2H, d, J = 8.5 Hz), 7.58 (2H, d, J = 8.5 Hz), 8.15 (1H, s), 8.27

(1H, s).

Example 667

Preparation of 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carboxylic acid phenylamide

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (100 mg, 0.30 mmol) was suspended in DMF (5 ml). To the suspension, triethylamine (43 μl, 0.31 mmol) and phenylisocyanate (34 μl, 0.31 mmol) were added followed by stirring at room temperature for 30 minutes. To the reaction mixture, water was added followed by stirring, and the precipitates were filtered off. The precipitates were purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and recrystallized from ethyl acetate, filtered off to afford 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carboxylic acid phenylamide (90 mg, yield 88%) as a white powder.

MS; 343(M^+)

Melting point 229-232°C (decomposition).

Using pyridine 4-isocyanate or benzyl isocyanate gave compounds of Examples 668 and 669 in the same manner as in Example 667.

Example 668

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carboxylic acid 4-pyridinamide

Melting point 217-219°C.

Example 669

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carboxylic acid benzylamide

Melting point 244-247°C (decomposition).

Example 670

Preparation of tert-butyl 4-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-ylcarbonyl)piperazine-1-carboxylate

Triphosgene (227 mg, 0.77 mmol) was dissolved in toluene (10 ml). To the solution, tert-butyl piperazine-1-carboxylate (425 mg, 2.28 mmol) and diisopropylethylamine (0.4 ml, 2.28 mmol) were added followed by stirring for 1 hour with cooling on ice-bath. To the solution, 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (700 mg, 2.07 mmol) was added. The solution was stirred at room temperature for 1 hour and then stirred under reflux for 1 hour. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/acetone = 10/1) and then crystallized from methylene chloride-diisopropyl ether to afford tert-

butyl 4-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-ylcarbonyl)piperazine-1-carboxylate (342 mg, yield 38%) as a white powder.

Melting point 260.0-265.0°C (decomposition).

^{1}H-NMR ($CDCl_3$) δppm:

1.47 (9H, s), 1.90 - 2.02 (2H, m), 2.10 - 2.16 (2H, m), 3.23 - 3.47 (10H, m), 3.60 - 3.66 (2H, m), 3.96 (2H, s), 7.54 (1H, s).

Using 4-trifluoromethylbenzyl piperazine-1-carboxylate or 1-(4-trifluoromethylbenzyl)piperazine gave compounds of Examples 671 and 672 in the same manner as in Example 670.

Example 671

4-Trifluoromethylbenzyl 4-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-ylcarbonyl)piperazine-1-carboxylate

Melting point 221-223°C.

Example 672

1-(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-ylcarbonyl)-4-(4-trifluoromethylbenzyl)piperazine

Melting point 226-230°C (decomposition).

Example 673

Preparation of 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-carboxylic acid 4-(dimethylamino)phenylamide

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in

Example 655 (200 mg, 0.59 mmol) was suspended in DMF (5 ml). To the suspension, triethylamine (0.1 ml, 0.72 mmol) was added followed by stirring. To the solution, a mixture of N,N-dimethyl-p-phenylenediamine (132 mg, 0.98 mmol), 1,1'-carbonyldiimidazole (82.7 mg, 1.02 mmol) and DMF (5 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature for 30 minutes. To the reaction mixture, water was added followed by stirring, and the precipitates were filtered off. The precipitates were purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from ethyl acetate to afford 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carboxylic acid 4-(dimethylamino)phenylamide (181 mg, yield 79%) as a white powder.

MS 386(M^+)

Melting point 244-247°C (decomposition).

Using 4-trifluoromethylbenzylamine or 4-trifluoromethoxybenzylamine gave compounds of Examples 674 and 675 in the same manner as in Example 673.

Example 674

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carboxylic acid 4-trifluoromethyl-benzylamide

Melting point 215-217°C.

Example 675

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-

piperidine]-1'-carboxylic acid 4-trifluoromethoxy-benzylamide

Melting point 223-225°C.

Example 676

Preparation of 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carbothioic acid 4-chlorophenylamide

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (200 mg, 0.59 mmol) was suspended in DMF (5 ml). To the suspension, triethylamine (0.24 ml, 1.77 mmol) and 4-chlorophenyl isothiocyanate(200 mg, 1.18 mmol) were added followed by stirring at room temperature for 30 minutes. To the reaction mixture, water was added followed by stirring, and the precipitates were filtered off, purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from methylene chloride-diisopropyl ether to afford 2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-carbothioic acid 4-chlorophenylamide (222 mg, yield 87%) as a white powder.

^{1}H-NMR (DMSO-d_6) δppm:

2.02 - 2.19 (4H, m), 3.59 - 3.69 (2H, m), 4.19 (2H, s), 4.40 - 4.54 (2H, m), 7.30 - 7.37 (4H, m), 8.18 (1H, s), 9.48 (1H, s).

Example 677

Preparation of 4-[(2,3-dihydro-6-nitrospiro[imidazo-

[2,1-b]oxazole-2,4'-piperidin])-1'-ylcarbonyl]amino-benzoic acid

Tert-butyl 4-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylcarbonyl]aminobenzoate (150 mg, 0.68 mmol) was dissolved in methylene chloride (1 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was crystallized from methanol-ethyl acetate to afford 4-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylcarbonyl]aminobenzoic acid (59 mg, yield 45%) as a white powder.

Melting point >300°C.

^{1}H-NMR (DMSO-d_6) δppm:

1.92 - 2.12 (4H, m), 3.32 - 3.39 (2H, m), 3.86 - 3.95 (2H, m), 4.17 (2H, s), 7.45 (2H, d, J = 8.8 Hz), 7.82 (2H, d, J = 8.8 Hz), 8.17 (1H, s), 8.97 (1H, s), 12.54 (1H, s).

Example 678

Preparation of 2-[(2,3-dihydro-6-nitrospiro[imidazo-[2,1-b]oxazole-2,4'-piperidin])-1'-yl]benzothiazole

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (84 mg, 0.25 mmol) was suspended in DMF (3 ml). To the suspension, triethylamine (76 µl, 0.55 mmol) and 2-chlorobenzothiazole (40 µl, 0.30 mmol) were

added followed by stirring at 80°C for 1 hour. The reaction mixture was concentrated under reduced pressure. To the residue, water was added, and the precipitate was filtered off, crystallized from methylene chloride-methanol to afford 2-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine])-1'-yl]benzothiazole (55 mg, yield 62%) as a white powder.

MS; 357(M^+)

^{1}H-NMR (DMSO-d_6) δppm:

2.05 - 2.23 (4H, m), 3.52 - 3.63 (2H, m), 3.89 - 3.97 (2H, m), 4.18 (2H, s), 7.05 - 7.12 (1H, m), 7.26 - 7.32 (1H, m), 7.46 - 7.49 (1H, m), 7.76 - 7.80 (1H, m), 8.18 (1H, s).

Using 5-chloro-1-phenyl-1H-tetrazole gave the compound of Example 679 in the same manner as in Example 678.

Example 679

5-[(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-yl]-1-phenyl-1H-tetrazole

^{1}H-NMR (DMSO-d_6) δppm:

2.05 - 2.09. (4H, m), 3.24 - 3.40 (4H, m), 4.14 (2H, s), 7.59 - 7.72 (5H, m), 8.15 (1H, s).

Example 680

Preparation of tert-butyl 4-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylacetyl]piperazine-1-carboxylate

2,3-Dihydro-6-nitrospiro[imidazo[2,1-

b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (700 mg, 2.07 mmol) was suspended in DMF (20 ml). To the suspension, tert-butyl 4-(chloroacetyl)piperazine-1-carboxylate (599 mg, 2.28 mmol), N,N-diisopropylethylamine (0.8 ml, 4.57 mmol) and sodium iodide (310 mg, 2.07 mmol) were added followed by stirring at 100°C for 3 hours. The reaction mixture was allowed to return to room temperature. To the solution, ethyl acetate and water were added followed by stirring vigorously. The precipitates were filtered off, washed with water and ethyl acetate, and then dried under reduced pressure to afford tert-butyl 4-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylacetyl]piperazine-1-carboxylate (688 mg, yield 74%) as a white powder.

Melting point >300°C.

^{1}H-NMR (DMSO-d_6) δppm:

1.41 (9H, s), 1.95 - 2.01 (4H, m), 2.43 - 2.64 (4H, m), 3.21 (2H, s), 3.26 - 3.42 (6H, m), 3.50 - 3.52 (2H, m), 4.12 (2H, s), 8.14 (1H, s).

Using 2-chloro-N-(4-trifluoromethylphenyl)-acetamide or 3-(3-chloropropyl)-3H-benzoxazol-2-one gave compounds of Examples 681 and 682 in the same manner as in Example 680.

Example 681

(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylacetic acid (4-trifluoromethylphenyl)-amide

Melting point 273-275°C (decomposition).

Example 682

3-[3-(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-yl]propyl-3H-benzoxazol-2-one

Melting point 190-192°C.

Example 683

Preparation of tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate

2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine] trifluoroacetate prepared in Example 655 (200 mg, 0.59 mmol) was suspended in DMF (5 ml). To the suspension, tert-butyl 4-(2-chloroethyl)piperazine-1-carboxylate (150 mg, 0.60 mmol), triethylamine (0.25 ml, 1.79 mmol) and sodium iodide (108 mg, 0.72 mmol) were added followed by stirring at 50°C for 5 hours. The reaction mixture was allowed to return to room temperature. To the solution, ethyl acetate and water were added followed by stirring vigorously. The precipitates were filtered off, washed with water and ethyl acetate, and then dried under reduced pressure to afford tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate (80 mg, yield 31%) as a white powder.

Melting point 214-215°C.

Example 684

Preparation of 4-trifluromethylbenzyl 4-[2-(2,3-

dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate

Tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazol-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate prepared in Example 653 (300 mg, 0.67 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure. To the residue, methylene chloride (1 ml) and triethylamine (1 ml) were added. The reaction mixture was stirred at room temperature for 5 minutes and concentrated under reduced pressure, and the residue was dissolved in DMF (15 ml). To the solution, a mixture of 4-trifluoromethylbenzyl alcohol (293 mg, 1.67 mmol), 1,1'-carbonyldiimidazole (270 mg, 1.67 mmol) and DMF (5 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate, and the organic phase was washed with a saturated saline solution and dried over magnesium sulfate. After filtration, the resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford 4-trifluromethylbenzyl 4-[2-(2,3-

dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate (324 mg, yield 88%) as a light pink powder.

MS 553$(M+H)^+$

Melting point 139.0-141.0°C.

Using corresponding starting materials gave the compound of Example 685 in the same manner as in Example 684.

Example 685

4-Trifluoromethoxybenzyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate

Melting point 137-139°C.

Using tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate prepared in Example 683 gave compounds of Examples 686 to 689 in the same manner as in Example 684.

Example 686

4-Chlorobenzyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo-[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate

Melting point 178-179°C.

Example 687

4-Trifluoromethylbenzyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate

Melting point 174-175°C.

Example 688

4-Trifluoromethoxybenzyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate

Melting point 176-177°C.

Example 689

Biphenyl-4-ylmethyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylethyl]piperazine-1-carboxylate

^{1}H-NMR ($CDCl_3$) δppm:

1.90 - 2.05 (2H, m), 2.15 - 2.20 (2H, m), 2.40 - 2.80 (12H, m), 3.45 - 3.60 (4H, m), 3.99 (2H, s), 5.17 (2H, s), 7.31 - 7.62 (10H, m).

Using tert-butyl 4-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-ylacetyl)piperazine-1-carboxylate prepared in Example 680 gave the compound of Example 690 in the same manner as in Example 684.

Example 690

4-Trifluoromethylbenzyl 4-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-ylacetyl]piperazine-1-carboxylate

Melting point 137-139°C.

Example 691

Preparation of 1-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-yl)-2-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]ethanone

Tert-butyl 4-[2-(2,3-dihydro-6-

nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate prepared in Example 653 (300 mg, 0.67 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (10 ml) was added followed by stirring at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure. To the solution, methylene chloride (1 ml) and triethylamine (1 ml) were added followed by stirring at room temperature for 5 minutes. The solution was concentrated under reduced pressure and the residue was dissolved in methanol (10 ml). To the solution, 4-trifluoromethylbenzaldehyde (0.23 ml, 1.67 mmol), sodium cyanotrihydroborate (105 mg, 1.67 mmol) and acetic acid (0.1 ml) were added with cooling on ice-bath followed by stirring at room temperature overnight. To the solution, a saturated aqueous sodium hydrogencarbonate solution and methylene chloride were added followed by stirring. The organic phase was dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 50/1) and crystallized from methylene chloride-diisopropyl ether to afford 1-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin])-1'-yl)-2-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]ethanone (226 mg, yield 67%) as a white powder.

MS 508(M)$^+$

Melting point 145-147°C.

Using corresponding starting materials gave the compound of Example 692 in the same manner as in Example 691.

Example 692

1-(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-[(4-phenylbenzyl)piperazin-1-yl]ethanone

Melting point 187-188°C.

Using tert-butyl 4-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-ylacetyl)piperazine-1-carboxylate prepared in Example 680 gave compounds of Examples 693 and 694 in the same manner as in Example 691.

Example 693

1-(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-ylacetyl)-4-(4-trifluoromethyl-benzyl)piperazine

Melting point 195-197°C (decomposition).

Example 694

1-(2,3-Dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-ylacetyl)-4-(4-phenylbenzyl)piperazine

Melting point 226-227°C (decomposition).

Example 695

Preparation of 4-[(2,3-dihydro-6-nitrospiro[imidazo-[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-oxoethyl]-piperazine-1-carboxylic acid (4-trifluoromethyl-

phenyl)amide

Tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate prepared in Example 653 (300 mg, 0.67 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (10 ml) was added followed by stirring at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure. To the solution, methylene chloride (1 ml) and triethylamine (1 ml) were added followed by stirring at room temperature for 5 minutes. The solution was concentrated under reduced pressure, and the residue was dissolved in DMF (10 ml). To the solution, a mixture of 4-aminobenzotrifluoride (0.17 ml, 1.33 mmol) and 1,1'-carbonyldiimidazole (220 mg, 1.33 mmol) and DMF (5 ml) stirred at room temperature for 3 hours was added followed by stirring at room temperature for 2 hours. The reaction mixture was poured into water and extracted with ethyl acetate, and the organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 200/1) and crystallized from methylene chloride-isopropyl ether to afford 4-[(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-

piperidin]-1'-yl)-2-oxoethyl]piperazine-1-carboxylic acid (4-trifluoromethylphenyl)amide (213 mg, yield 59%) as a white powder.

Melting point 153.0-155.0°C.

Example 696

Preparation of 2-{4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazin-1-yl}-N-(4-trifluoromethylphenyl)acetamide

Tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazol-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate prepared in Example 653 (300 mg, 0.67 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (10 ml) was added followed by stirring at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure. To the residue, methylene chloride (1 ml) and triethylamine (1 ml) were added followed by stirring at room temperature for 5 minutes, and then the solution was concentrated under reduced pressure. The residue was dissolved in DMF (10 ml). To the solution, 2-bromo-N-(4-trifluoromethylphenyl)acetamide (207 mg, 0.73 mmol) and triethylamine (0.28 ml, 2.0 mmol) were added followed by stirring at 100°C for 2 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with a saturated saline solution, dried over magnesium sulfate and then

filtered. The resulting filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 100/1) and crystallized from methylene chloride-diisopropyl ether to afford 2-{4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)-2-oxoethyl]piperazin-1-yl}-N-[4-trifluoromethylphenyl]acetamide (275 mg, yield 75%) as a white powder.

MS 552$(M+1)^+$

Melting point 133.0-135.0°C.

Example 697

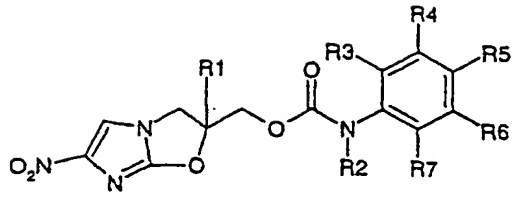
Preparation of 2-[4-(benzoxazol-2-yl)piperazin-1-yl]-1-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)ethanone

Tert-butyl 4-[2-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidine]-1'-yl)-2-oxoethyl]piperazine-1-carboxylate prepared in Example 653 (227 mg, 0.50 mmol) was dissolved in methylene chloride (5 ml). To the solution, trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure. To the residue, methylene chloride (1 ml) and triethylamine (1 ml) were added followed by stirring at room temperature for 5 minutes, and then the solution was concentrated under reduced pressure. The residue was dissolved in DMF (5 ml). To the solution,

triethylamine (0.21 ml, 1.52 mmol) and 2-chlorobenzoxazole (86 μl, 0.76 mmol) were added followed by stirring at 80°C for 2 hours. To the reaction mixture, water was added, and the mixture was extracted with methylene chloride. The organic phase was dried over magnesium sulfate and then filtered. The resulting filtrate was concentrated under reduced pressure. The residue was crystallized from methylene chloride-ethyl acetate to afford 2-[4-(benzoxazol-2-yl)piperazin-1-yl]-1-(2,3-dihydro-6-nitrospiro[imidazo[2,1-b]oxazole-2,4'-piperidin]-1'-yl)ethanone (99 mg, 42%) as a light yellow powder.
MS 467(M^+)
Melting point 260.0-263.0°C (decomposition).

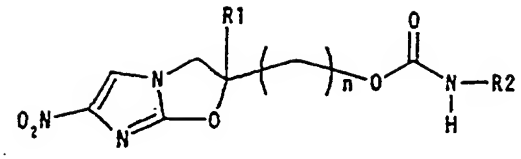
Compounds gave from appropriate starting materials in the same manner as in the above Examples 1 to 697 are shown in the following tables 26 to 77.

Table 26



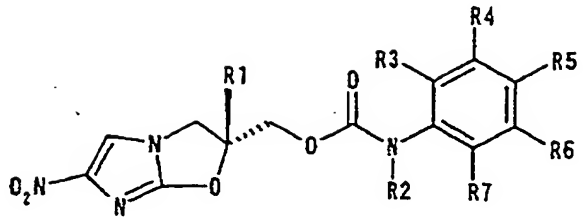
Example	R1	R2	R3	R4	R5	R6	R7	mp(°C)	
698	-H	-H	-H	-H	$-CH_3$	-H	-H	193-195	
699	-H	-H	-H	-H	$-CO_2C_2H_5$	-H	-H	195-197.5	
700	-H	-H	-H	-H	$-OCH_3$	-H	-H	189-190	
701	-H	-H	-H	-H	-Cl	-Cl	-H	182-183	
702	-H	-H	-H	-H	-H	-H	-H	185-186	
703	$-CH_3$	-H	-H	-H	$-OCH_3$	-H	-H	177.5 - 179	
704	$-CH_3$	-H	-H	-H	-F	-H	-H	194-196	
705	$-CH_3$	-H	-H	-H	$-CH_3$	-H	-H	145-147	
706	$-CH_3$	-H	-H	-H	-H	-Cl	-H	190.5-192	
707	$-CH_3$	-H	-H	-H	-H	-H	-Cl	163-164	
708	$-CH_3$	-H	-H	-H	-H	-H	$-OCH_3$	177-180	
709	$-CH_3$	-H	-H	-H	-H	$-CF_3$	-H	182-183.5	
710	$-CH_3$	-H	-H	$-OCH_3$	$-OCH_3$	$-OCH_3$	-H	179-182	
711	$-CH_3$	-H	-H	-H	-H	-H	-F	142 - 144	
712	$-CH_3$	-H	-H	-H	-Br	-H	-H	197 - 199	
713	$-CH_3$	-H	-H	-H	$-CONH_2$	-H	-H	234 - 235	dec
714	$-CH_3$	-H	-H	-H	$-CO_2C_2H_5$	-H	-H	151 - 152	
715	$-CH_3$	-H	-H	-H	$-COCH_3$	-H	-H	196 - 199	
716	$-CH_3$	-H	-H	-H	$-SO_2NH_2$	-H	-H	218 - 220	dec
717	$-CH_3$	-H	-H	-H	-H	$-CO_2C_2H_5$	-H	112 - 114	
718	$-CH_3$	-H	-H	-H	-H	-H	$-CO_2C_2H_5$	132 - 134	
719	$-CH_3$	$-CH_3$	-H	-H	-Br	-H	-H	132 - 133	
720	$-CH_3$	-H	-H	-H	$-CF_3$	-H	-H	198.5 - 200	
721	$-CH_3$	-H	-H	-H	$-OCF_3$	-H	-H	163.5 - 164.8	
722	$-CH_3$	$-CH_3$	-H	-H	$-CF_3$	-H	-H	129 - 130	
723	$-CH_3$	$-CH_3$	-H	-H	$-OCF_3$	-H	-H	138 - 140	
724	$-CH_3$	-H	-H	-H	Morpholino-	-H	-H	223-225	
725	$-CH_3$	-H	-H	-H	Morpholino-	-H	-H	134-135	
726	$-CH_3$	-H	-H	-H	$C_6H_{13}NHCO-$	-H	-H	197-198	

Table 27



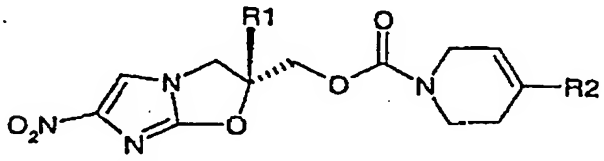
Example	n	R1	R2	mp(°C) or 1H NMR
727	1	-H	$-CH_2Ph$	143.5-145
728	1	-H	-cyclo-C_6H_{11}	187-188.5
729	1	$-CH_3$	$-CH_2Ph$	141 - 142
730	1	$-CH_3$	$-(CH_2)_2Ph$	124 - 127
731	1	$-CH_3$	-cyclo-C_6H_{11}	176 - 178
732	1	$-CH_3$	-4-PYRIDYL	151 – 153 (dec)
733	1	$-CH_3$	$-CH(CH_3)_2$	163 - 165
734	1	$-CH_3$	$-CH_2CO_2C_2H_5$	142 - 143
735	1	$-CH_3$	$-C_6H_{13}$	129 - 130
736	1	$-CH_3$	$-(CH_2)_2CO_2C_2H_5$	94 - 96
737	1	$-CH_3$	$-CH_2CH_2Cl$	DMSO-d_6, 1.59(3H, s), 3.22-3.33(2H, m), 3.57(2H, t, J=6.0Hz), 4.07(2H, dd, J=11.1Hz, 27.6Hz), 4.27(2H, dd, J=7.6Hz, 9.9Hz), 6.47-6.59(1H, m), 8.13(1H, s)
738	1	-H	$-C_8H_{17}$	DMSO-d6, 0.85(3H, t, J=6.9Hz), 1.00-1.45(12H, m), 2.90-2.98(2H, m), 4.06(1H, dd, J=6.8Hz, 10.8Hz), 4.25-4.46(3H, m), 5.48-5.66(1H, m), 7.28(1H, t, J=5.6Hz), 8.13(1H, s)
739	2	-H	C_8H_{17}-	86-88
740	2	$-CH_3$	Ph-	131-133
741	2	$-CH_3$	$PhCH_2$-	127-127.5
742	2	$-CH_3$	$PhCH_2CH_2$-	124-125

Table 28



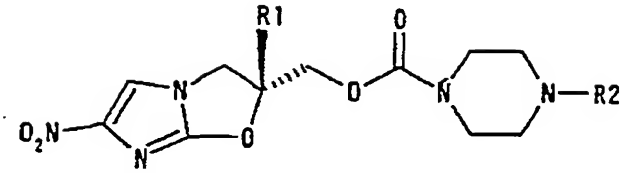
Example	R1	R2	R3	R4	R5	R6	R7	mp(°C)
743	$-CH_3$	$-CH_3$	-H	-H	-H	-Cl	-H	103 - 104
744	$-CH_3$	$-CH_2Ph$	-H	-H	-Cl	-H	-H	168 - 169
745	$-CH_3$	$-C_6H_{13}$	-H	-H	-Cl	-H	-H	98 - 100
746	$-CH_3$	$-CH_3$	-H	-H	-Br	-H	-H	147 - 150
747	$-CH_3$	$-CH_3$	-H	-H	$-CF_3$	-H	-H	140 - 141
748	$-CH_3$	$-CH_3$	-H	-H	-F	-H	-H	111 - 113
749	$-CH_3$	$-C_4H_9$	-H	-H	-Cl	-H	-H	114 - 116
750	$-CH_3$	$-C_2H_5$	-H	-H	-Cl	-H	-H	87 - 89
751	$-CH_3$	$-CH_2CH(CH_3)_2$	-H	-H	-Cl	-H	-H	161 - 165
752	$-CH_3$	4-ClPhCH_2-	-H	-H	-Cl	-H	-H	175 - 178

Table 29



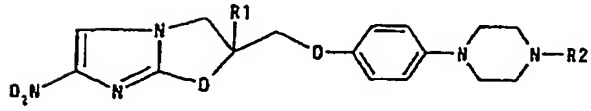
Example	R1	R2	mp(°C)
753	$-CH_3$	4-CF_3OPh-	165 - 166
754	$-CH_3$	4-CH_3OPh-	155 - 157
755	$-CH_3$	4-ClPh-	157 - 158
756	$-CH_3$	3-CF_3Ph-	100 - 101
757	$-CH_3$	4-BrPh-	168 - 170
758	$-CH_3$	4-FPh-	151 - 154

Table 30



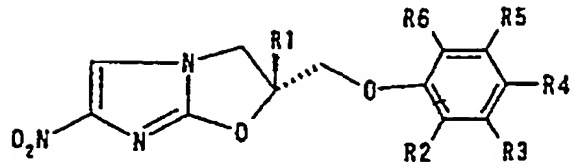
Example	R1	R2	mp(°C)
759	-CH_3	4-CF_3Ph-	151 – 153
760	-CH_3	4-ClPh-	143 – 144
761	-CH_3	3-ClPh-	136 – 138
762	-CH_3	3,4-Cl_2Ph-	142 – 143
763	-CH_3	4-CH_3OPh-	163 – 164
764	-CH_3	3-CF_3Ph-	105 – 107
765	-CH_3	4-FPh-	139 – 140
766	-CH_3	4-CF_3OPhCH_2OCO-	166 – 167
767	-CH_3	4-CF_3PhCH=CHCH_2OCO-	186 – 188
768	-CH_3	4-CF_3PhCH_2-	205 – 206
769	-CH_3	4-CF_3OPhCH_2-	133 – 134

Table 31



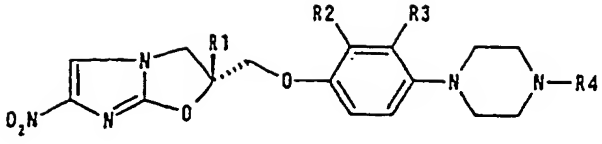
Example	R1	R2	mp(°C) or 1H NMR
770	-CH_3	4-ClPh-	228.8 - 232.2
771	-CH_3	4-CF_3OPh-	236.2 - 237.4
772	-CH_3	4-CF_3OPhCH_2-	$CDCl_3$; 1.76(3H ,s), 3.03(4H, br), 3.62-3.67(4H, m), 4.01(1H, d, J=10.2Hz), 4.04(1H, d, J=10.2Hz), 4.18(1H, d, J=10.2Hz), 4.48(1H, d, J=10.2Hz), 5.15(2H, s), 6.76-6.80(2H, m), 6.85-6.89(2H, m), 7.19-7.23(2H, m), 7.38-7.42(2H, m), 7.54(1H, s)
773	-CH_3	4-Cl$PhCH_2$-	174.2 - 175
774	-CH_3	4-CF_3OPhCH_2OCO-	155.5 - 156.5
775	-CH_3	4-CF_3PhCH=CHCH_2OCO-	155 – 159.8

Table 32



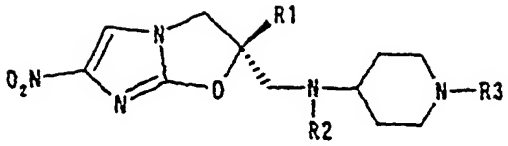
Example	R1	R2	R3	R4	R5	R6	mp(°C)	
776	$-CH_3$	-H	-H	-H	-H	-H	151 - 153.5	
777	$-CH_3$	-H	-H	-I	-H	-H	220 - 221	
778	$-CH_3$	-H	-H	-Cl	-H	-H	185 - 186.5	
779	$-CH_3$	-H	-H	Morpholino-	-H	-H	233 - 240	dec
780	$-CH_3$	-H	-H	Piperidino-	-H	-H	217 - 218.5	dec

Table 33



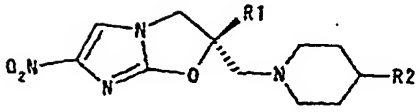
Example	R1	R2	R3	R4	mp(°C) or 1H NMR
781	$-CH_3$	-H	-H	$-CH_3$	230 - 231.5 dec
782	$-CH_3$	-H	-Cl	$-CH_3$	201 - 204.5 dec
783	$-CH_3$	-H	-H	4-CF_3Ph-	258 – 259 dec
784	$-CH_3$	-H	-H	4-$ClPhCH_2$-	207 - 208.4
785	$-CH_3$	-H	-H	4-ClPh-	251 – 257 dec
786	$-CH_3$	-H	-H	CH_3CO-	206 - 207.5
787	$-CH_3$	-H	-Cl	C_2H_5OCO-	168.5 - 171
788	$-CH_3$	-Cl	-H	t-BuOCO-	192 - 194.5
789	$-CH_3$	-Cl	-H	C_2H_5OCO-	178.5 - 180.5
790	$-CH_3$	-Cl	-Cl	t-BuOCO-	233 - 233.5 dec
791	$-CH_3$	-Cl	-Cl	C_2H_5OCO-	224.2 - 225.7
792	$-CH_3$	-H	-H	$-CO_2CH_2CF_3$	213 - 216
793	$-CH_3$	-H	-H	$-CO_2C_4H_9$	197.5 - 199
794	$-CH_3$	-H	-H	$-CO_2(CH_2)_7CH_3$	198 - 201
795	$-CH_3$	-H	-H	$-CO_2(CH_2)_2OCH_3$	176 - 179
796	$-CH_3$	-H	-Cl	4-CF_3OPhCH_2OCO-	153 - 155
797	$-CH_3$	-Cl	-H	4-CF_3OPhCH_2OCO-	176 - 176.8
798	$-CH_3$	-Cl	-Cl	4-CF_3OPhCH_2OCO-	196.5 - 197.5
799	$-CH_3$	-H	-H	4-$CF_3OPhCH2OCO$-	187 - 189
800	$-CH_3$	-H	-H	4-CF_3PhCH_2OCO-	180.5 - 182.5
801	$-CH_3$	-H	-H	4-$CF_3PhCH=CHCH_2OCO$-	185 - 187
802	$-CH_3$	-H	-H	3,4-Cl_2PhCH_2OCO-	171 - 171.5
803	$-CH_3$	-H	-H	4-$CF_3OPhNHCO$-	228 – 232 dec
804	$-CH_3$	-H	-H	$-CO_2(CH_2)_2N(CH_3)_2$	$CDCl_3$: 1.76(3H ,s), 2.30(6H, s), 2.61(2H, t, J=5.8Hz), 2.99-3.04(4H, m), 3.60-3.64(4H, m), 4.03(1H, d, J=10.2Hz), 4.04(1H, d, J=10.1Hz), 4.18(1H, d, J=10.1Hz), 4.22(2H, t, J=5.8Hz), 4.49(1H, d, J=10.2Hz), 6.76-6.81(2H, m), 6.83-6.89(2H, m), 7.55(1H, s)

Table 34



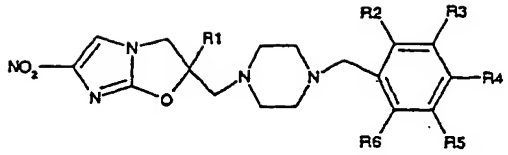
Example	R1	R2	R3	mp(°C)
805	-CH_3	-CH_3	4-CF_3OPh-	127.2 - 129.7
806	-CH_3	-CH_3	4-CF_3Ph-	131.5 - 133.6
807	-CH_3	-CH_3	4-NCPh-	149 - 152
808	-CH_3	-CH_3	4-CF_3OPhCH_2OCO-	84.2 - 86.8
809	-CH_3	-CH_3	4-$ClPhCH_2OCO$-	116.2 - 116.6

Table 35



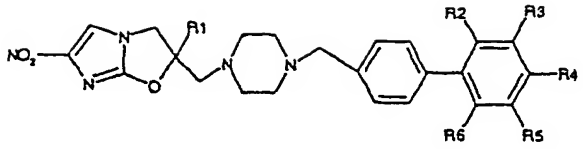
Example	R1	R2	mp(°C) or 1H NMR
810	-CH_3	-OPh	153.2 - 154.8
811	-CH_3	4-CF_3PhNH-	$CDCl_3$; 1.16-1.42(2H,m), 1.61(3H,s), 1.87-2.01(2H,m), 2.31-2.60(3H,m), 2.78-3.02(4H,m), 3.24-3.30(1H,m), 3.82(1H,d,J=8.1Hz), 3.91(1H,d,J=9.7Hz), 4.29(1H,d,J=9.7Hz), 6.54(2H,d,J=8.6Hz), 6.98-7.36(2H,d,J=8.6Hz), 7.54(1H,s)
812	-CH_3	4-CF_3Ph-	130 - 131.8
813	-CH_3	4-CF_3PhCH_2-	117.5 - 118.5
814	-CH_3	4-$ClPhCH_2$-	146.5-147.5
815	-CH_3	4-ClPhCO-	177 - 179
816	-CH_3	4-CF_3PhCO-	98 - 100
817	-CH_3	4-CF_3OPhO-	119.4 - 120.7
818	-CH_3	4-ClPhO-	141 - 144
819	-CH_3	3-CF_3PhO-	89 - 91.7
820	-CH_3	4-NCPhO-	171 - 174.7
821	-CH_3	4-FPhO-	124 - 128
822	-CH_3	4-CF_3OPhCH_2O-	113 - 115
823	-CH_3	4-$ClPhCH_2O$-	138 - 140
824	-CH_3	4-$PhPhCH_2O$-	115 - 116.5
825	-CH_3	$PhCH_2CH_2O$-	79 - 81
826	-CH_3	4-PyridylCH_2O-	80.8 - 83.9
827	-CH_3	3-PyridylCH_2O-	77 - 79
828	-CH_3	4-CF_3OPhCH_2OCO-	101 - 102
829	-CH_3	4-ClPhNHCO-	153 - 155
830	-CH_3	4-$ClPhCH_2NHCO$-	161 - 164
831	-CH_3	4-ClPhNH-	159 - 161
832	-CH_3	4-NCPhNH-	148.5 - 150
833	-CH_3	4-ClPhN(CH_3)-	180.2 - 181.1 dec
834	-CH_3	4-NCPhN(CH_3)-	188.5 - 191
835	-CH_3	4-CF3PhN(CH_3)-	161 - 164
836	-CH_3	(4-ClPh)$_2$N-	178.5 - 180

Table 36



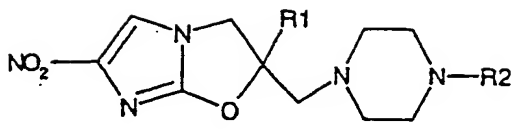
Example	R1	R2	R3	R4	R5	R6	mp(°C) or 1H NMR
837	$-CH_3$	-H	-H	$-CH(CH_3)_2$	-H	-H	158.5 - 160
838	$-CH_3$	-H	-Cl	-Cl	-H	-H	115 - 117.9
839	$-CH_3$	-H	-H	$-CF_3$	-H	-H	126 - 129.2
840	-H	-H	-H	$-CF_3$	-H	-H	164 - 166
841	$-CH_3$	-H	-H	-OPh	-H	-H	157 - 158.2
842	$-CH_3$	-H	$-OCH_3$	$-OCH_3$	$-OCH_3$	-H	147 - 151.9
843	$-CH_3$	-H	-H	$-CO_2CH_3$	-H	-H	151 - 152.5
844	$-CH_3$	-H	-H	-3-PYRIDYL	-H	-H	140 - 143.8
845	$-CH_3$	-H	-Ph	-H	-H	-H	94.6 - 96.5
846	$-CH_3$	-H	-H	-cyclo-C_6H_{11}	-H	-H	162 - 163.9
847	$-CH_3$	-Ph	-H	-H	-H	-H	146.8 - 149
848	$-CH_3$	-H	-H	-CH=CHPh	-H	-H	178.5 - 181.8
849	$-CH_3$	-H	$-CF_3$	-H	$-CF_3$	-H	154 - 156.2
850	$-CH_3$	-H	-H	-H	-H	-H	$CDCl_3$, 1.59(3H, s), 2.34(4H, bs), 2.50-2.59(2H, m), 2.53(1H, d, J=14.8Hz), 2.67-2.76(2H, m), 2.85(1H, d, J=14.8Hz), 3.41(1H, d, J=12.9Hz), 3.47(1H, d, J=12.9Hz), 3.87(1H, d, J=9.6Hz), 4.30(1H, d, J=9.6Hz), 7.23-7.33(5H, m), 7.53(1H, s)
851	$-CH_3$	-H	-H	$-N(CH_3)_2$	-H	-H	$CDCl_3$ 1.58(3H, s), 2.30(4H, br), 2.49-2.57(2H, m), 2.52(1H, d, J=14.9Hz), 2.65-2.73(2H, m), 2.84(1H, d, J=14.9Hz), 2.93(6H, s), 3.34(2H, d, J=3.50Hz), 3.86(1H, d, J=9.6Hz), 4.30(1H, d, J=9.6Hz), 6.67(2H, d, J=8.7Hz), 7.11(2H, d, J=8.7Hz), 7.52(1H, s)
852	$-CH_3$	-H	-H	$-OCH_3$	-H	-H	$CDCl_3$, 1.59(3H, s), 2.31(4H, br), 2.50-2.58(2H, m), 2.53(1H, d, J=14.8Hz), 2.65-2.74(2H, m), 2.84(1H, d, J=14.8Hz), 3.35(1H, d, J=13.0Hz), 3.41(1H, d, J=13.0Hz), 3.79(3H, s), 3.88(1H, d, J=9.7Hz), 4.30(1H, d, J=9.7Hz), 6.83(2H, d, J=8.6Hz), 7.17(2H, d, J=8.6Hz), 7.52(1H, s)
853	$-CH_3$	-H	-H	$-CH_2Ph$	-H	-H	$CDCl_3$ 1.61(3H, s), 2.30-2.73(9H, m), 2.84(1H, d, J = 14.8Hz), 3.49(2H, s), 3.87(1H, d, J = 9.7Hz), 3.95(2H, s), 4.30(1H, d, J = 9.7Hz), 7.09-7.33(9H, m), 7.52(1H, s)

Table 37



Example	R1	R2	R3	R4	R5	R6	mp(°C) or 1H NMR
854	$-CH_3$	-H	-H	-Cl	-H	-H	176.8 - 181.3
855	$-CH_3$	-H	-H	-Cl	-Cl	-H	111.8 - 114.8
856	$-CH_3$	-H	-H	$-OCH_3$	-H	-H	183.3 - 186.6
857	$-CH_3$	-H	-H	-H	-H	-Cl	123.5 - 125.3
858	$-CH_3$	-H	-H	-H	-H	-H	$CDCl_3$; 1.59(3H, s), 2.37(4H, bs), 2.51-2.61(2H, m), 2.54(1H, d, J=14.8Hz), 2.69-2.76(2H, m), 2.86(1H, d, J=14.8Hz), 3.44(1H, d, J=13.1Hz), 3.51(1H, d, J=13.1Hz), 3.88(1H, d, J=9.6Hz), 4.31(1H, d, J=9.6Hz),7.29-7.36(3H, m) 7.39-7.47(2H, m), 7.51-7.60(4Hm), 7.53(1H, s)
859	$-CH_3$	-H	-H	$-CF_3$	-H	-H	$CDCl_3$; 1.60(3H, s), 2.37-2.75(9H, m), 2.87(1H, d, J=14.9Hz), 3.49(2H, s),.3.88(1H, d, J=9.6Hz), 4.30(1H, d, J=9.6Hz), 7.37(1H, d, J=8.0Hz), 7.53(1H, s), 7.54(1H, d, J=8.0Hz), 7.68(4H, s)
860	$-CH_3$	-H	-H	$-OCF_3$	-H	-H	$CDCl_3$; 1.60(3H, s), 2.38(4H, br), 2.55(1H, d, J=14.9Hz), 2.60(2H, br), 2.71-2.76(2H, m), 2.87(1H, d, J=14.9Hz), 3.50(2H, s), 3.89(1H, d, J=9.7Hz), 4.30(1H, d, J=9.7Hz), 7.27(2H, d, J=6.6Hz), 7.36(2H, d, J=8.1), 7.47-7.52(2H, m), 7.53(1H, s), 7.55-7.61(2H, m)

Table 38



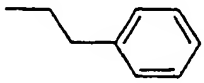
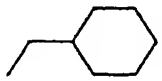
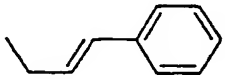
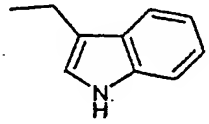
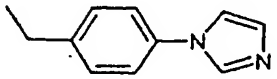
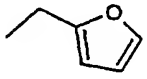
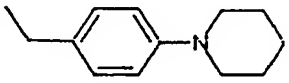
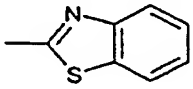
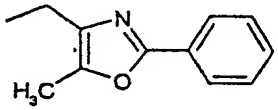
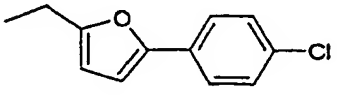
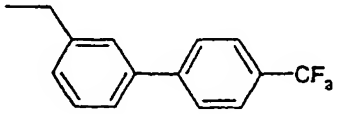
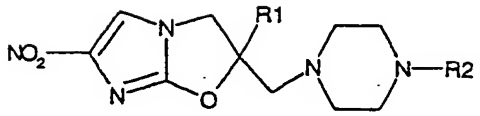
Example	R1	R2	mp(°C)
861	-CH_3		134 - 138.8
862	-CH_3		188.6 - 190.7
863	-CH_3		127 - 131.5
864	-CH_3		156 - 158.6
865	-CH_3		102.8-104.9
866	-CH_3		129 - 133
867	-CH_3		164.0-168.5
868	-CH_3		221.5 - 222.3
869	-CH_3		158 - 159.4
870	-CH_3		105 - 107
871	-CH_3		142 - 145.4

Table 39



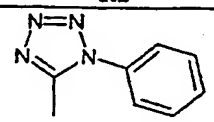
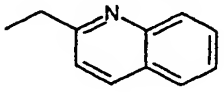
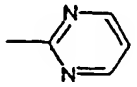
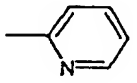
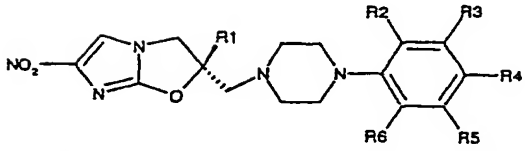
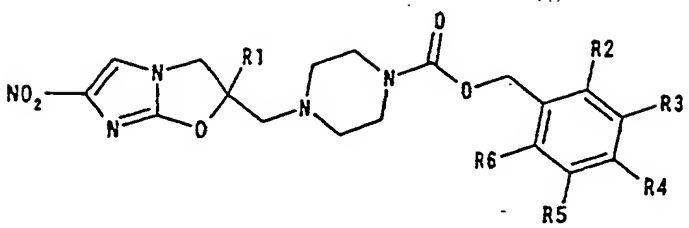
Example	R1	R2	mp(°C)
872	-CH_3		196 - 199.4
873	-CH_3		102 – 104
874	-CH_3		215.5 - 217
875	-CH_3		195 - 197.8

Table 40



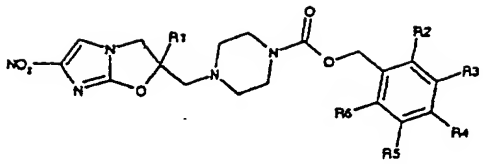
Example	R1	R2	R3	R4	R5	R6	mp(°C) or 1H NMR
876	-H	-H	-H	-CF_3	-H	-H	175.8 - 176.6
877	-CH_3	-H	-H	-H	-H	-H	180.6 - 184.2
878	-CH_3	-H	-H	-F	-H	-H	175 - 179.5
879	-CH_3	-H	-H	-OCH_3	-H	-H	172 - 172.5
880	-CH_3	-H	-H	-$CO_2C_2H_5$	-H	-H	175 - 179.2
881	-CH_3	-H	-H	-CH_3	-H	-H	185 - 185.5
882	-CH_3	-H	-H	-Cl	-Cl	-H	177 - 177.3
883	-CH_3	-H	-H	-H	-CF_3	-H	171.6 - 173.6
884	-CH_3	-H	-H	-H	-H	-CF_3	179.5 - 180.3
885	-CH_3	-H	-H	-Cl	-CF_3	-H	170.5 - 171.2
886	-CH_3	-H	-H	-CO_2H	-H	-H	248 - 252
887	-CH_3	-H	-H	-H	-H	-F	191 - 192.2
888	-CH_3	-H	-H	-$N(CH_3)_2$	-H	-H	206 - 207
889	-H	-H	-H	-F	-H	-H	178.5 - 179.5
890	-H	-H	-H	-CN	-H	-H	211 - 211.5
891	-H	-H	-H	-Cl	-H	-H	183 - 183.5
892	-CH_3	-H	-H	-CF_3	-H	-H	$CDCl_3$: 1.64(3H, s), 2.59-2.75(2H, m), 2.62(1H, d, J=15Hz), 2.80-2.95(2H, m), 2.93(1H, d, J=15Hz), 3.00-3.25(4H, m), 3.94(1H, d, J=10Hz), 4.35(1H, d, J=10Hz), 6.86(2H, d, J=8Hz), 7.46(2H, d, J=8Hz), 7.53(1H, s)
893	-CH_3	-H	-H	-$CO_2C(CH_3)_3$	-H	-H	198.5 – 200.5

Table 41



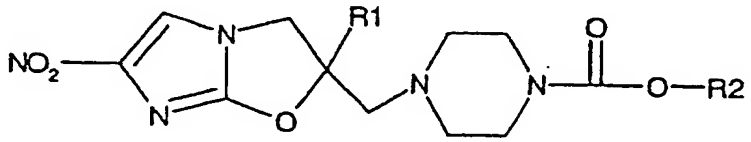
Example	R1	R2	R3	R4	R5	R6	mp(°C)
894	$-CH_3$	-H	-H	-Cl	-H	-H	144.2 - 145.6
895	$-CH_3$	-H	-H	$-OCF_3$	-H	-H	153 - 156.9
896	$-CH_3$	-H	-H	-Cl	-Cl	-H	114.5 - 116.6
897	$-CH_3$	-H	-H	-H	-Cl	-H	132.4 - 136.3
898	$-CH_3$	-H	-H	-H	-H	-Cl	143.5 - 145
899	$-CH_3$	-H	-H	-Br	-H	-H	151 - 152
900	$-CH_3$	-H	-H	-Ph	-H	-H	134 - 135.2
901	$-CH_3$	-H	-H	$-CO_2CH_3$	-H	-H	127 - 130.5
902	$-CH_3$	-H	-H	$-OCH_3$	-H	-H	128 - 130
903	$-CH_3$	-H	-H	$-OCH_2Ph$	-H	-H	128 - 131
904	$-CH_3$	-Cl	-H	-H	-H	-Cl	142 - 145.5
905	$-CH_3$	-H	-Cl	-H	-Cl	-H	132 - 135.3
906	$-CH_3$	-H	-H	-H	$-CF_3$	-H	117 - 118
907	$-CH_3$	-H	-H	$-CH_3$	-H	-H	117 - 118
908	$-CH_3$	-H	-H	-H	$-OCH_3$	-H	106 - 108
909	$-CH_3$	-H	-H	-H	-H	$-CH_3$	143 - 145
910	$-CH_3$	-H	-H	-H	-H	$-OCH_3$	127 - 130
911	$-CH_3$	-H	-H	-H	-H	$-CF_3$	144 - 145
912	$-CH_3$	-H	-H	$-OC_4H_9$	-H	-H	126 - 127
913	$-CH_3$	-H	-H	$-NO_2$	-H	-H	156 - 158
914	$-CH_3$	-H	$-CF_3$	-H	$-CF_3$	-H	159 - 160
915	$-CH_3$	-H	-H	-CN	-H	-H	125 - 129
916	$-CH_3$	-H	-H	$-C(CH_3)_3$	-H	-H	147 - 149
917	$-CH_3$	-H	-H	-H	$-CH_3$	-H	125 - 127
918	$-CH_3$	-H	-H	$-CH_3$	$-CH_3$	-H	135 - 138
919	$-CH_3$	-H	-H	$-OCH_3$	$-OCH_3$	-H	149 - 151
920	$-CH_3$	-H	-H	-H	-H	-F	131 - 133
921	$-CH_3$	-H	-H	$-C_2H_5$	-H	-H	144 - 146
922	$-CH_3$	-H	-H	$-SO_2CH_3$	-H	-H	112 - 115
923	$-CH_3$	-H	-H	$-CON(CH_3)_2$	-H	-H	108 - 111
924	$-CH_3$	-H	-H	$-CONHC_3H_7$	-H	-H	124 - 126
925	$-CH_3$	-H	-H	$-OCH(CH_3)_2$	-H	-H	122 - 123
926	$-CH_3$	-H	-H	$-OSO_2CH_3$	-H	-H	100 - 104
927	$-CH_3$	-H	-H	-I	-H	-H	132 - 134
928	$-CH_3$	-H	-H	$-NHCOCH_3$	-H	-H	105 - 109
929	$-CH_3$	-H	-H	$-CONH_2$	-H	-H	159 - 161
930	$-CH_3$	-H	-H	-F	-Cl	-H	148 - 149

Table 42



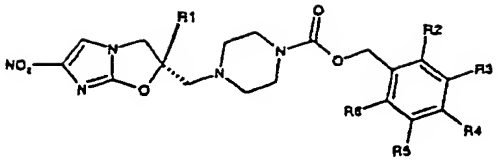
Example	R1	R2	R3	R4	R5	R6	mp(°C) or 1H NMR
931	-CH_3	-H	-H	-F	-H	-H	$CDCl_3$ 1.62(3H, s), 2.38-2.70(4H, bm), 2.56(1H, d, J=14.9Hz), 2.87(1H, d, J=14.9Hz), 3.41(4H, bs), 3.92(1H, d, J=9.7Hz), 4.28(1H, d, J=9.7Hz), 5.06(2H, s), 6.99-7.07(2H, m), 7.28-7.34(2H, m), 7.53(1H, s)
932	-CH_3	-H	-H	-CF_3	-H	-H	$CDCl_3$ 1.62(3H, s), 2.45-2.75(4H, bm); 2.58(1H, d, J=14.9Hz), 2.86(1H, d, J=14.9Hz), 3.20-3.60(4H, br), 3.94(1H, d, J=9.8Hz), 4.29(1H, d, J=9.8Hz), 5.15(2H, s), 7.44(1H, d, J=8.0Hz), 7.54(1H, s), 7.61(1H, d, J=8.0Hz)
933	-CH_3	-H	-H	-OH	-H	-H	$CDCl_3$ 1.59(3H, s), 2.30-2.70(4H, m), 2.56(1H, d, J=15Hz), 2.86(1H, d, J=15Hz), 3.10-3.55(4H, m), 3.91(1H, d, J=10Hz), 4.28(1H, d, J=10Hz), 5.03(2H, s), 5.30(1H, brs), 6.84(2H, d, J=8Hz), 7.24(2H, d, J=8Hz), 7.53(1H, s)
934	-CH_3	-H	-H	-NH_2	-H	-H	$CDCl_3$ 1.61(3H, s), 2.35-2.70(4H, m), 2.56(1H, d, J=15Hz), 2.85(1H, d, J=15Hz), 3.05-3.55(4H, m), 3.69(2H, brs), 3.91(1H, d, J=10Hz), 4.28(1H, d, J=10Hz), 4.98(2H, s), 6.55(2H, d, J=8Hz), 7.14(2H, d, J=8Hz), 7.53(1H, s)
935	-CH_3	-H	-H	$(CH_3)_3C(CH_3)_2Si$-	-H	-H	114 – 115
936	-CH_3	-H	-H	$(CH_3)_3COCONH$-	-H	-H	124 - 127

Table 43



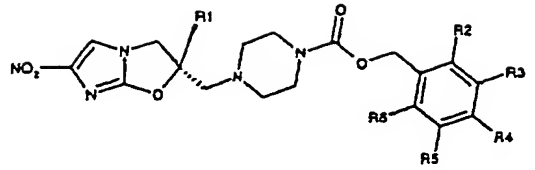
Example	R1	R2	mp(°C)
937	-CH_3	-$(CH_2)_2Ph$	143.5 - 144.6
938	-CH_3	4-$ClPh(CH_2)_2$-	118 – 119
939	-CH_3	4-$ClPhCH{=}CHCH_2$-	121 – 123.3
940	-CH_3	4-$CF_3PhCH{=}CHCH_2$-	121 – 122
941	-CH_3	4-$CF_3OPhCH{=}CHCH_2$-	127 – 128

Table 44



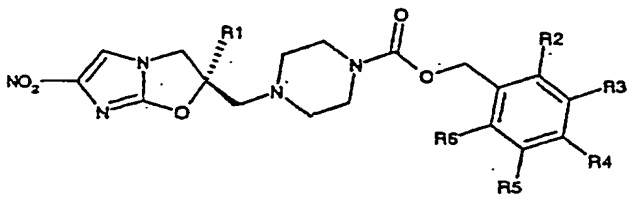
Example	R1	R2	R3	R4	R5	R6	mp(°C) or 1H NMR
942	$-CH_3$	-H	-H	-H	-Cl	-H	83 - 85
943	$-CH_3$	-H	-H	-F	-H	-H	174 - 175
944	$-CH_3$	-H	-H	-H	-H	$-CH_3$	187 - 188.5
945	$-CH_3$	-H	-H	-H	-H	-H	163.5 - 165.5
946	$-CH_3$	-H	-H	-Cl	-H	-H	172.5 - 174
947	-H	-H	-H	$-OCF_3$	-H	-H	128 - 129
948	$-CH_3$	-H	-H	-Cl	-Cl	-H	97 - 98
949	$-CH_3$	-H	-H	-F	-F	-H	115 - 116
950	$-CH_3$	-H	-H	-H	-F	-F	101 - 103
951	$-CH_3$	-H	-F	-H	-F	-H	85 - 87
952	$-CH_3$	-F	-F	-F	-F	-F	143 - 144
953	$-CH_3$	-F	-H	-F	-H	-F	92 - 95
954	$-CH_3$	-H	-F	-H	-H	-F	144 - 146
955	$-CH_3$	-F	-H	-H	-H	-F	169 - 170
956	$-CH_3$	-H	-H	-F	-H	-F	178 - 182
957	$-CH_3$	-H	-H	-H	-F	-H	112 - 115
958	$-CH_3$	-H	-H	-H	$-CF_3$	-H	78 - 80
959	$-CH_3$	-H	-H	-H	-H	-F	175 - 176
960	$-CH_3$	-H	-H	-Br	-H	-H	166 - 167
961	-H	-H	-H	-F	-H	-H	121.5 - 122
962	-H	-H	-H	-Cl	-H	-H	112.9 - 116.7
963	-H	-H	-H	-Cl	-Cl	-H	105.5 - 106
964	-H	-H	-H	-H	-Cl	-H	97.5 - 98
965	-H	-H	-H	-H	-F	-H	93 - 94
966	$-CH_3$	-H	-H	$-OCHF_2$	-H	-H	134 - 135
967	$-CH_3$	-H	-H	-F	$-OCH_3$	-F	71 - 74
968	$-CH_3$	-H	-H	-F	$-OCHF_2$	-F	84 - 86
969	$-CH_3$	-H	-H	-Cl	$-OCHF_2$	-H	85 - 87
970	$-CH_3$	-H	-H	-Cl	-H	-H	180 - 181
971	$-CH_3$	-H	-H	$-CF_3$	-H	-H	185 - 187
972	$-CH_3$	-H	-H	$-OCF_3$	-H	-H	172 - 173
973	$-CH_3$	-H	-H	$-OCH_2CF_3$	-H	-H	76 - 80
974	$-CH_3$	-H	-H	-Cl	$-OCH_2CF_3$	-H	139 - 140

Table 45



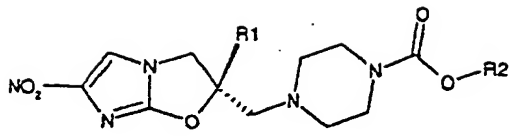
Example	R1	R2	R3	R4	R5	R6	mp(°C) or 1H NMR
975	-CH_3	-H	-H	-OCH_2CF_3	-Cl	-H	$CDCl_3$ 1.62(3H, s), 2.40-2.75(4H, m), 2.57(1H, d, J=15Hz), 2.87(1H, d, J=15Hz), 3.05-3.50(4H, m), 3.92(1H, d, J=10Hz), 4.28(1H, d, J=10Hz), 4.40(2H, q, J=8Hz), 5.02(2H, s), 6.40(2H, d, J=8Hz), 7.21(2H, dd, J=8,2Hz), 7.39(1H, d, J=2Hz), 7.53(1H, s)
976	-CH_3	-H	-H	-$OCHF_2$	-Cl	-H	$CDCl_3$ 1.62(3H, s), 2.40-2.70(4H, m), 2.59(1H, d, J=15Hz), 2.87(1H, d, J=15Hz), 3.10-3.55(4H, m), 3.96(1H, d, J=10Hz), 4.30(1H, d, J=10Hz), 5.13(2H, s), 6.53(1H, t, J=73Hz), 7.10-7.30(2H, m), 7.42(1H, s), 7.55(1H, s)
977	-CH_3	-H	-H	-Br	-$OCHF_2$	-F	$CDCl_3$ 1.62(3H, s), 2.40-2.65(4H, m), 2.59(1H, d, J=15Hz), 2.86(1H, d, J=15Hz), 3.00-3.50(4H, m), 3.96(1H, d, J=10Hz), 4.29(1H, d, J=10Hz), 5.14(2H, s), 6.59(1H, t, J=73Hz), 7.17(1H, m), 7.39(1H, m), 7.55(1H, s)

Table 46



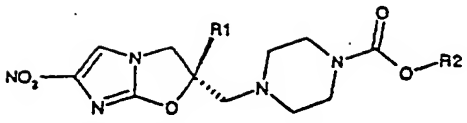
Example	R1	R2	R3	R4	R5	R6	mp(°C)
978	-CH_3	-H	-H	-CF_3	-H	-H	139.8 - 141.7
979	-CH_3	-H	-H	-H	-Cl	-H	108 - 111
980	-CH_3	-H	-H	-H	-H	-CH_3	185 - 186
981	-CH_3	-H	-H	-Cl	-CF_3	-H	115 - 115.5
982	-CH_3	-H	-H	-CF_3	-CH_3	-H	91 - 91.5
983	-CH_3	-H	-H	-SCF_3	-H	-H	136.5 - 137
984	-CH_3	-H	-H	-F	-Cl	-H	72.5 - 73
985	-CH_3	-H	-H	-Cl	-H	-CH_3	178.5 - 179

Table 47



Example	R1	R2	mp(°C)
986	-CH_3	-CH_2-cyclo-C_6H_{11}	101 - 103
987	-CH_3	-cyclo-C_6H_{11}	189.6 - 191.6
988	-CH_3	-CH_2CF_3	123.5 - 124
989	-CH_3	-$CH_2CH=C(CH_3)_2$	138 - 138.5
990	-CH_3	(E)-3,4-Cl_2PhCH=$CHCH_2$-	145 - 148
991	-CH_3	(E)-4-ClPhCH=$CHCH_2$-	124 - 125
992	-CH_3	(E)-4-CF_3OPhCH=$CHCH_2$-	60 - 61
993	-H	(E)-4-ClPhCH=$CHCH_2$-	113 - 114
994	-H	(E)-4-ClPhC(CH_3)=$CHCH_2$-	109 - 110
995	-H	(Z)-4-ClPhC(CH_3)=$CHCH_2$-	95 - 96
996	-CH_3	(E)-4-CF_3PhCH=$CHCH_2$-	132 - 133
997	-CH_3	(Z)-4-CF_3PhCH=$CHCH_2$-	138 - 140
998	-CH_3	(E)-3-CF_3-4-ClPhCH=$CHCH_2$-	147 - 149
999	-CH_3	(E)-4-FPhCH=$CHCH_2$-	155 - 156
1000	-CH_3	(E)-4-CF_3PhCH=C(CH_3)CH_2-	122 - 123
1001	-CH_3	(4-CF_3Ph)$_2$C=$CHCH_2$-	145 - 146
1002	-CH_3	4-ClPh(CH_2)$_2$-	150 - 151
1003	-CH_3	4-ClPh(CH_2)$_3$-	96 - 97
1004	-CH_3	4-ClPh(CH_2)$_4$-	78 - 82
1005	-CH_3	4-ClPhO(CH_2)$_2$-	138 - 139
1006	-CH_3	4-CF_3OPh(CH_2)$_3$-	46 - 48
1007	-CH_3	4-CF_3Ph(CH_2)$_3$-	118 - 120
1008	-CH_3	4-CF_3PhO(CH_2)$_2$-	104 - 108
1009	-CH_3	4-CF_3OPhN(CH_3)(CH_2)$_2$-	102 - 104
1010	-CH_3	(E)-4-ClPhC(CH_3)=CHCH2-	$CDCl_3$ 1.62(3H, s), 2.02-2.10(3H, m), 2.57(1H, d, J=14.9Hz), 2.40-2.73(4H, m), 2.87(1H, d, J=14.9Hz), 3.06-3.62(4H, m), 3.93(1H, d, J=9.7Hz), 4.29(1H, d, J=9.7Hz), 4.76(2H, m), 5.87(1H, dt, J=1.3Hz, 6.7Hz), 7.23-7.37(4H, m), 7.54(1H, s)
1011	-CH_3	(Z)-4-ClPhC(CH_3)=CHCH2-	$CDCl_3$ 1.62(3H, s), 2.02-2.10(3H, m), 2.58(1H, d, J=14.9Hz), 2.35-2.72(4H, m), 2.86(1H, d, J=14.9Hz), 3.04-3.56(4H, m), 3.94(1H, d, J=9.8Hz), 4.30(1H, d, J=9.8Hz), 4.46(2H, m), 5.66(1H, dt, J=1.4Hz, 7.0Hz), 7.04-7.12(2H, m), 7.23-7.35(2H, m), 7.53(1H, s)

Table 48



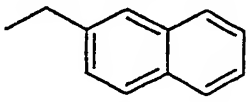
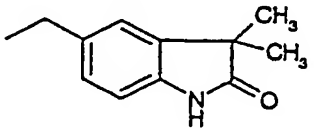
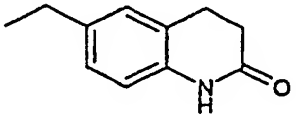
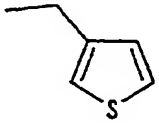
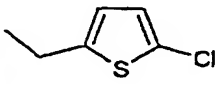
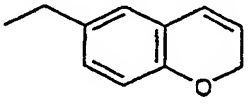
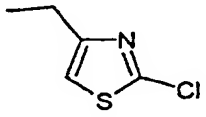
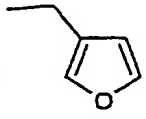
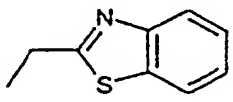
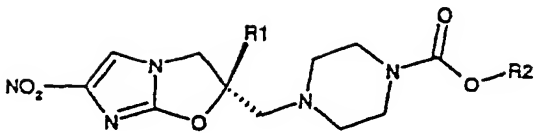
Example	R1	R2	mp(°C)
1012	-CH_3		80 - 85
1013	-CH_3		120 - 140
1014	-CH_3		189 - 190
1015	-CH_3		196.1 - 199.1
1016	-CH_3		137.4 - 139.2
1017	-CH_3		71 - 76.4
1018	-CH_3		121.1 - 122.1
1019	-CH_3		177.1 - 178.9
1020	-CH_3		158.5 - 160.4

Table 49



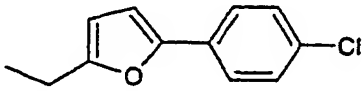
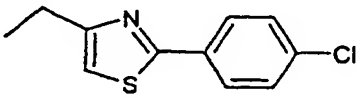
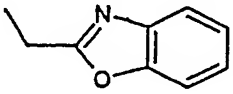
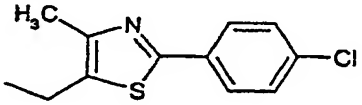
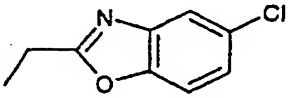
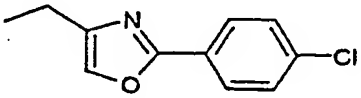
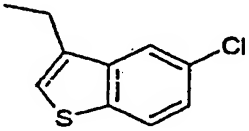
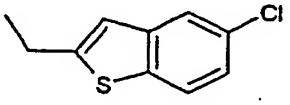
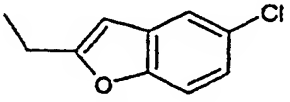
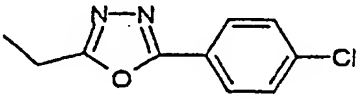
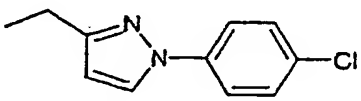
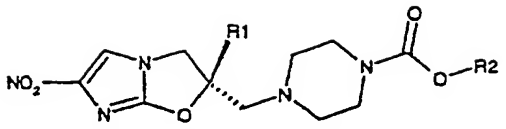
Example	R1	R2	mp(°C)
1021	-CH_3		193.4 - 195.9
1022	-CH_3		203.6 - 204.9
1023	-CH_3		89.7 - 91.8
1024	-CH_3		185.2 - 187.5
1025	-CH_3		93.6 - 96.5
1026	-CH_3		215.3 - 216.4
1027	-CH_3		180.7 - 182.3
1028	-CH_3		170.2 - 170.6
1029	-CH_3		134.3 - 135.7
1030	-CH_3		83.6 - 86.3
1031	-CH_3		191.8 - 192.9

Table 50



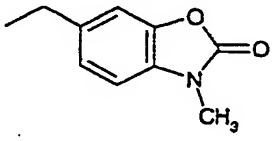
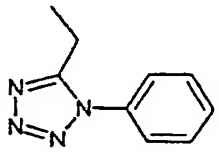
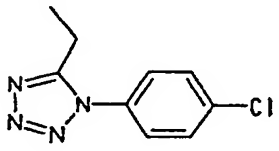
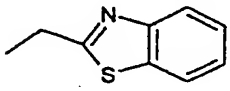
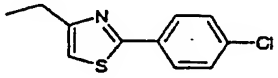
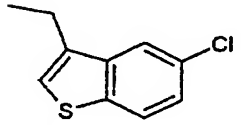
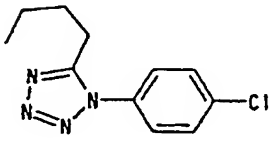
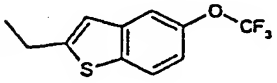
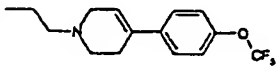
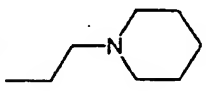
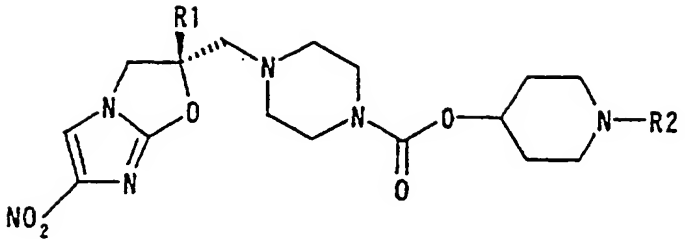
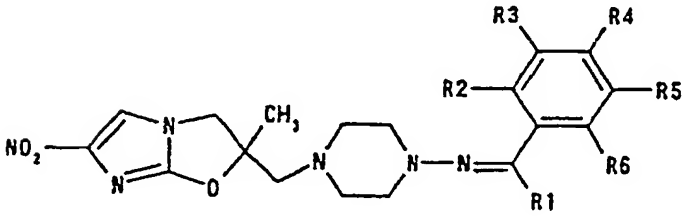
Example	R1	R2	mp(°C) or 1H NMR
1032	-CH_3		174.3 - 179.2
1033	-CH_3		108.9 - 113.1
1034	-CH_3		193.5 - 194.7
1035	-H		152 - 153.5
1036	-H		190.3 - 191.2
1037	-H		177.5 - 180.9
1038	-CH_3		127.5 - 128.1
1039	-CH_3		140 - 141.5
1040	-CH_3		114 - 117
1041	-CH_3		$CDCl_3$ 1.40-1.62(5H, m), 1.80-1.93(2H, br), 2.46-2.64(13H, m), 2.87(1H, d, J=14.9Hz), 3.37(4H, br), 3.92(1H, d, J=9.7Hz), 4.20(2H, t, J=6.1), 7.53(1H, s)

Table 51



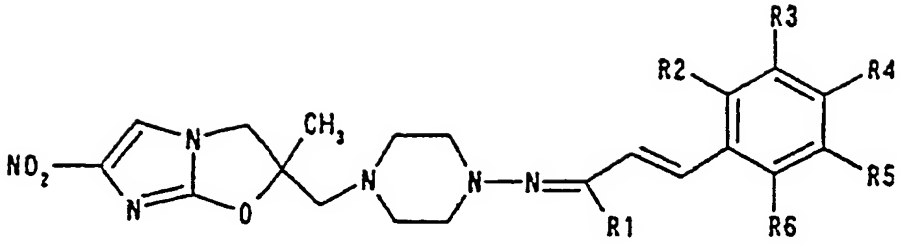
Example	R1	R2	mp(°C)
1042	-CH_3	4-CF_3OPh-	160.5 - 161.4
1043	-CH_3	4-CF_3Ph-	158.6 - 160.6
1044	-CH_3	4-CH_3OPh-	138.5 - 139.5
1045	-CH_3	Ph-	163 - 163.5
1046	-CH_3	4-FPh-	159 - 160
1047	-CH_3	$PhCH_2$-	141.5 - 142
1048	-CH_3	4-ClPh-	177 - 178
1049	-CH_3	4-NCPh-	158 - 159
1050	-CH_3	4-Cl$PhCH_2$-	144 - 145
1051	-CH_3	4-CF_3PhCH_2-	95.5 - 97
1052	-CH_3	4-CF_3OPhCH_2-	143 - 143.5
1053	-CH_3	4-CF_3PhCO-	160.5 - 162.4
1054	-CH_3	4-ClPhCO-	218 - 220.3
1055	-CH_3	4-CF_3OPhCO-	169.8 - 172.7

Table 52



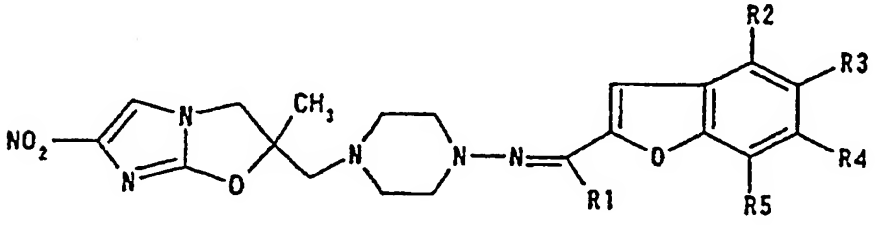
Example	R1	R2	R3	R4	R5	R6	Mp(°C)
1056	-H	-H	-H	-CF_3	-H	-H	215.3 - 217.8
1057	-H	-H	-H	-Br	-H	-H	219.2 - 221.3
1058	-H	-F	-H	-Br	-H	-H	198.8 - 200.5
1059	-H	-H	-F	-Cl	-H	-H	199 - 199.5
1060	-H	-H	-H	-CN	-H	-H	180.2 - 184.1
1061	-H	-F	-F	-F	-H	-H	188.5 - 189.2
1062	-H	-H	-F	-F	-F	-H	191.7 - 192.6
1063	-H	-F	-H	-Cl	-H	-H	202.8 - 203.3

Table 53



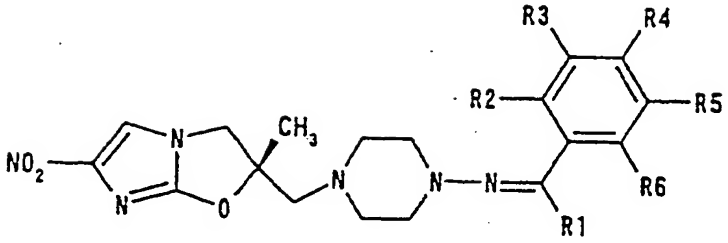
Example	R1	R2	R3	R4	R5	R6	mp(°C)
1064	-H	-H	-H	-Cl	-H	-H	214.2 - 214.8
1065	-H	-H	-Cl	-Cl	-H	-H	204.1 - 205.7
1066	-H	-H	$-CF_3$	-H	-H	-H	127.8 - 131.8
1067	-H	-H	-H	$-OCF_3$	-H	-H	204.2 - 205.3
1068	-H	-H	-H	-F	-H	-H	199.2 - 200.2

Table 54



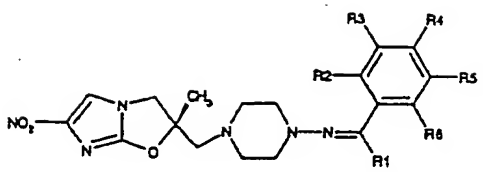
Example	R1	R2	R3	R4	R5	mp(°C)
1069	-H	-H	-Cl	-H	-H	164.6 - 165.9
1070	-H	-H	$-CF_3$	-H	-H	194.9 - 196
1071	-H	-H	$-OCF_3$	-H	-H	211.7 - 212.1
1072	-H	-H	-H	$-CF_3$	-H	182.9 - 185.9

Table 55



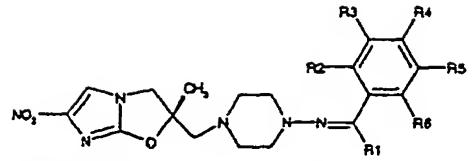
Example	R1	R2	R3	R4	R5	R6	mp(°C)
1073	-H	-H	-H	-F	-H	-H	202.5 - 203.1
1074	-H	-H	-H	$-OCH_3$	-H	-H	205.4 - 206.4
1075	-H	-H	-H	-Cl	-H	-Cl	162.7 - 164
1076	-H	-H	-H	-Cl	-H	-H	233.7 - 236.2
1077	-H	-H	-H	-1-PYRRYL	-H	-H	249.1 - 249.7
1078	-H	-H	-H	-Ph	-H	-H	211.6 - 212
1079	-H	-H	-H	$-OCH_2Ph$	-H	-H	202.2 - 203.9
1080	-H	-H	-H	-Br	-H	-H	224.4 - 226.2
1081	-H	-H	-H	$-OC_8H_{17}$	-H	-H	156.8 - 158.3
1082	-H	-H	-H	-CN	-H	-H	197.8 - 198.7
1083	-H	-H	-H	-OPh	-H	-H	198.1 - 200.1
1084	-H	-H	-F	-F	-F	-H	193.8 - 196
1085	-H	$-CH_3$	-H	$-CH_3$	-H	$-CH_3$	177.9 - 178.3
1086	-H	$-CH_3$	-H	-H	-H	$-CH_3$	175.7 - 178.2
1087	-H	-H	$-CF_3$	-H	$-CF_3$	-H	200.2 - 202.3
1088	-H	-H	-H	-Cl	-F	-H	197.2 - 199.2
1089	-H	-H	-H	-Br	-H	-F	206.1 - 207.4
1090	-H	-H	-H	-F	-F	-F	174 - 174.7
1091	-H	-H	-H	-Cl	-H	-F	202.8 - 203.7
1092	-H	-H	-H	$-C_4H_3$	-H	-H	162.2 - 165.1
1093	-H	-H	-H	$-N(Ph)_2$	-H	-H	182.6 - 186.4
1094	-H	-H	-H	-H	-Cl	-Cl	223.5 - 224.5
1095	-H	-H	-H	-I	-H	-H	217 - 221.1
1096	-H	-H	-H	-1-(1,2,4-triazolyl)	-H	-H	200.6 - 202.3

Table 56



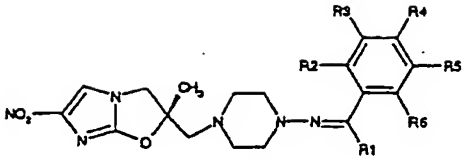
Example	R1	R2	R3	R4	R5	R6	MS
1097	-H	-H	-H	-H	-H	-H	370
1098	-H	-Cl	-H	-H	-H	-H	404
1099	-H	-H	-Cl	-H	-H	-H	404
1100	-H	-F	-H	-H	-H	-H	388
1101	-H	-H	-H	$-CH(CH_3)_2$	-H	-H	412
1102	-H	-H	-H	$-NO_2$	-H	-H	415
1103	-H	$-CF_3$	-H	-H	-H	-H	438
1104	-H	-H	$-CF_3$	-H	-H	-H	438
1105	-H	-H	-H	$-C(CH_3)_3$	-H	-H	426
1106	-H	-H	-H	$-OC_2H_5$	-H	-H	414
1107	-H	-Cl	-Cl	-H	-Cl	-H	472
1108	-H	-Cl	-Cl	-H	-H	-Cl	472
1109	-H	-H	-H	-H	-OPh	-H	462
1110	-H	-H	-F	-H	-H	-F	406
1111	-H	-F	-H	-F	-H	-H	406
1112	-H	-H	-H	-F	-F	-H	406
1113	-H	-H	-F	-H	-F	-H	406
1114	-H	-H	-H	-F	-F	-F	424
1115	-H	-H	-F	-H	-F	-F	424
1116	-H	-F	-H	-H	-F	-F	424
1117	-H	-H	-F	-F	-H	-F	424
1118	-H	-F	-H	-F	-H	-F	424
1119	-H	$-OCF_3$	-H	-H	-H	-H	454
1120	-H	-H	-H	$-C_2H_5$	-H	-H	398
1121	-H	-H	-H	-H	-Br	-H	448
1122	-H	-Br	-H	-H	-H	-H	448
1123	-H	-H	-H	-H	-F	-F	406
1124	-H	-Cl	-H	-H	-H	-Cl	438
1125	-H	$-OC_2H_5$	-H	-H	-H	-H	414
1126	-H	-H	-H	$-OC_4H_9$	-H	-H	442
1127	-H	-H	-H	-H	-H	$-OCH_2Ph$	476
1128	-H	-H	-H	-H	$-NO_2$	-H	415
1129	-H	-H	-H	-H	$-OCF_3$	-H	454
1130	-H	-H	-H	-Cl	-Cl	-H	438
1131	-H	-Cl	-H	-H	-Cl	-H	438
1132	-H	-H	-H	-H	$-OCOCH_3$	-H	428
1133	-H	$-NO_2$	-H	-H	-H	-H	415
1134	-H	-H	-H	-H	-F	-H	388
1135	-H	-H	-Cl	-H	-Cl	-H	438
1136	-H	-H	-H	-H	-CN	-H	395
1137	-H	-H	$-OCH_3$	-H	-H	-H	400
1138	-H	$-OCH_3$	$-OCH_3$	-H	-H	-H	430
1139	-H	$-OCH_3$	-H	$-OCH_3$	-H	-H	430
1140	-H	$-OCH_3$	-H	-H	$-OCH_3$	-H	430

Table 57



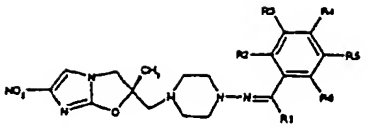
Example	R1	R2	R3	R4	R5	R6	MS
1141	-H	-H	-H	$-OCH_3$	$-OCH_3$	-H	430
1142	-H	-H	-H	$-OCH_3$	$-OCH_3$	$-OCH_3$	460
1143	-H	-H	-Cl	-H	-H	$-NO_2$	449
1144	-H	-H	-H	$-OCH_3$	-H	$-NO_2$	445
1145	-H	-H	$-OCH_3$	-H	-H	$-NO_2$	445
1146	-H	-H	-H	-H	-Ph	-H	446
1147	-H	$-NHSO_2CH_3$	-H	-H	-H	-H	463
1148	-H	-H	-H	$-CH_3$	-H	-H	384
1149	-H	-H	-H	$-CH_3$	$-CH_3$	-H	398
1150	-H	$-CH_3$	-H	$-CH_3$	-H	-H	398
1151	-H	-H	-H	-H	$-CH_3$	-H	384
1152	-H	-H	$-CH_3$	-H	-H	$-CH_3$	398
1153	-H	-H	-H	-H	-H	$-CH_3$	384
1154	-H	-H	-H	-H	$-CH_3$	$-CH_3$	398
1155	-H	-H	-H	$-OCOCH_3$	-H	-H	428
1156	-H	-H	-H	$-OC_3H_7$	-H	-H	428
1157	-H	-H	-H	$-NHCOCH_3$	-H	-H	427
1158	-H	-H	$-CH_3$	-H	$-CH_3$	-H	398
1159	-H	-H	$-CH_3$	$-CH_3$	-H	$-CH_3$	412
1160	-H	-H	-H	$-CO_2CH_3$	-H	-H	428
1161	-H	-H	-H	-CH=CHPh(trans)	-H	-H	472
1162	-H	-H	-H	$-N(CH_3)_2$	-H	-H	413
1163	-H	-H	-Br	-H	-H	$-OCH_3$	478
1164	-H	-H	-H	-F	-H	-Cl	422
1165	-H	-H	-Br	-H	-H	-F	466
1166	-H	-H	$-OCH_3$	-H	-H	-F	418
1167	-H	-H	-H	$-CH_2CH(CH_3)_2$	-H	-H	426
1168	-H	-Br	-H	$-OCH_3$	$-OCH_3$	-H	508
1169	-H	-F	-F	-F	-F	-F	460
1170	-H	-H	-H	$-N(CH_3)_2$	-H	$-OCH_3$	443
1171	-H	-H	$-OCH_2Ph$	-H	$-OCH_2Ph$	-H	582
1172	-H	-H	-H	$-OCH_2Ph$	$-OCH_2Ph$	-H	582
1173	-H	-H	-H	-H	$-OC_2H_5$	-H	414
1174	-H	-H	-H	-H	$-OCH_2Ph$	-H	476
1175	-H	-H	-H	$-OCH_2Ph$	$-OCH_3$	-H	506
1176	-H	-H	-H	$-SC_2H_6$	-H	-H	430
1177	-H	-H	-H	$-OCHF_2$	-H	-H	436
1178	-H	-H	-H	$-OCH(CH_3)_2$	-H	-H	428
1179	-H	-H	-H	$-OCH_3$	-Br	-H	478
1180	-H	-H	-H	$-N(C_2H_5)_2$	-H	-H	441
1181	-H	-H	-H	$-OCH_3$	-F	-H	418
1182	-H	-H	-H	$-OCH_3$	$-CH_3$	-H	414
1183	-H	$-OCH_3$	-H	-H	-F	-H	418
1184	-H	-Cl	-H	-H	$-NO_2$	-H	449

Table 58



Example	R1	R2	R3	R4	R5	R6	MS
1185	-H	-H	-H	$-OC_2H_5$	$-OC_2H_5$	-H	458
1186	-H	-H	-H	$-OCO\ CH_3$	$-OCH_3$	-H	458
1187	-H	$-NO_2$	-H	$-OCH_3$	$-OCH_3$	-H	475
1188	-H	-H	-H	$-SCH_3$	-H	-H	416
1189	-H	-H	-H	-Cl	$-NO_2$	-H	449
1190	-H	-H	-H	$-SO_2CH_3$	-H	-H	448
1191	-H	-H	-H	$-OCH_3$	$-OCH_2Ph$	-H	506
1192	-H	-H	-H	-Cl	$-CF_3$	-H	472
1193	-H	-I	-H	-H	-H	-H	496
1194	-H	-H	-H	-H	$-SCF_3$	-H	470
1195	-H	$-OCH_3$	-H	$-OCH_3$	$-OCH_3$	-H	460
1196	-H	-H	$-OCH_3$	-H	$-OCH_3$	-H	430
1197	-H	$-CO_2CH_3$	-H	-H	-H	-H	428
1198	-H	$-OCH_3$	-H	-H	-H	$-OCH_3$	430
1199	-H	$-OCH_3$	-H	$-OCH_3$	-H	$-OCH_3$	460
1200	-H	$-OCHF_2$	-H	-H	-H	-H	436
1201	-H	-H	-Br	$-OCH_3$	$-OCH_3$	-H	508
1202	-H	-H	$-CH_3$	$-OCH_3$	-H	$-CH_3$	428
1203	-H	-H	-H	-OH	-H	-H	386
1204	-H	-H	$-OCH_3$	-OH	$-OCH_3$	-H	446
1205	-H	-H	-H	-OH	-H	-OH	402
1206	-H	-H	-H	-H	-H	$-OCH_3$	400
1207	-H	-F	-H	-H	-H	-F	406
1208	-H	-H	-H	-3-PYRIDYL	-H	-H	447
1209	-H	-H	-H	$-OCH_2Ph$	-Cl	-H	510
1210	-H	-H	-H	-2-THIENYL	-H	-H	452
1211	-H	-H	$-OCH_3$	$-OCH_3$	$-OCH_3$	-H	460
1212	-H	-H	-H	$-cyclo-C_6H_{11}$	-H	-H	452
1213	-H	-H	-H	$CH_2=CHCH_2O-$	-H	-H	426
1214	-H	-H	-H	Pyrrolidinyl-	-H	-H	439
1215	-H	$EtOCOCH_2O-$	-H	-H	-H	-H	472
1216	-H	-H	-H	$-OCH_3$	$cyclo-C_3H_9O-$	-H	484
1217	-H	-H	CF_3CF_2O-	-H	-H	-H	504
1218	-H	-H	-H	Imidazolyl-	-H	-H	436
1219	-H	-H	-H	Piperidino-	-H	-H	453
1220	-H	-H	-H	$4-CF_3Ph-$	-H	-H	514
1221	-H	-H	-H	$4-CH_3OPh-$	-H	-H	476
1222	-H	-H	-H	$(CH_3)_2N(CH_2)_3O-$	-H	-H	471
1223	-H	-H	-H	Morpholino-	$-NO_2$	-H	500
1224	-H	-H	-H	Piperidino-	$-NO_2$	-H	498
1225	-H	-H	-H	4-FPh-	-H	-H	464
1226	-H	-H	-H	$4-CH_3(CH_2)_8Ph-$	-H	-H	572
1227	-H	-H	-H	$3,4-F_2Ph-$	-H	-H	482
1228	-H	-H	-H	$4-CH_3(CH_2)_3Ph-$	-H	-H	502
1229	-H	-H	-H	3-Cl-4-FPh-	-H	-H	498

Table 59



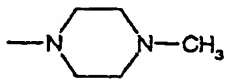
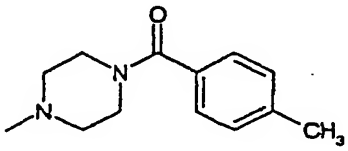
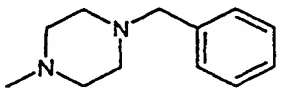
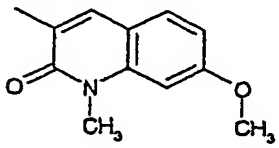
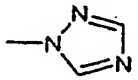
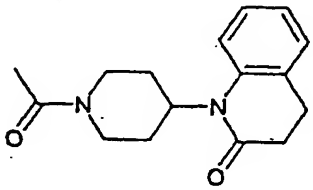
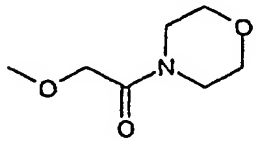
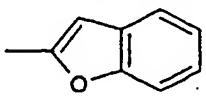
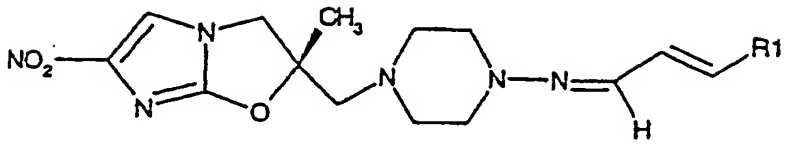
Example	R1	R2	R3	R4	R5	R6	MS
1230	-H	-H	-H	4-CF_3OPh-	-H	-H	530
1231	-H	-H	-H	4-CH_3Ph-	-H	-H	460
1232	-H	-H	-H	4-NCPh-	-H	-H	471
1233	-H	-H	-H	3,4-$(CH_3O)_2Ph$-	-H	-H	506
1234	-H		-OCH_2O-	-H	-H	-H	414
1235	-H	-H		-OCH_2O-	-H	-Cl	448
1236	-H	-H		-OCH_2O-	-H	-H	414
1237	-H	-H		-OCH_2O-	-OCH_3	-H	444
1238	-H	-NO_2	-H	-OCH_2O-		-H	459
1239	-H	-H	-H		-F	-H	486
1240	-H	-H		-H	-H	-NO2	617
1241	-H	-H		-H	-H	-NO2	589
1242	-H	-H		-H	-H	-OCH3	587
1243	-H	-H	-H		-H	-H	437
1244	-H	-H	-H		-H	-H	626
1245	-H	-H	-H		-H	-H	513
1246	-H	-H	-H		-H	-H	486

Table 60



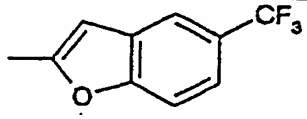
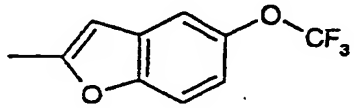
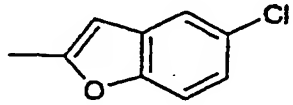
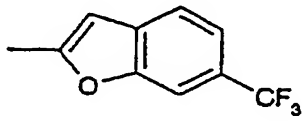
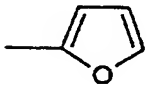
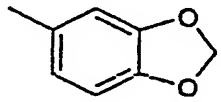
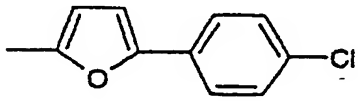
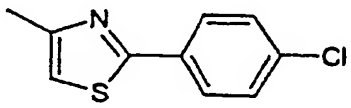
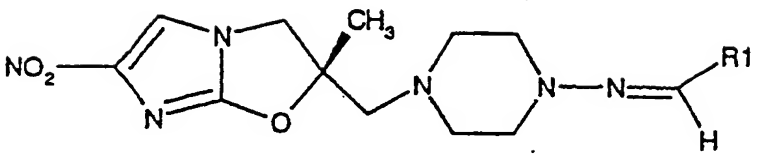
Example	R1	mp(°C) or MS
1247		174.1 - 175.8
1248		201.9 - 203
1249		218.8 - 220.1
1250		156 - 159.3
1251		386
1252		496
1253		513
1254		440

Table 61



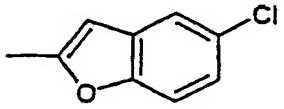
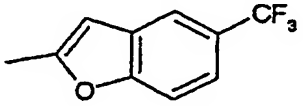
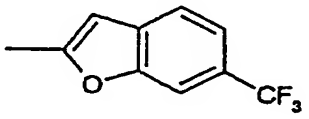
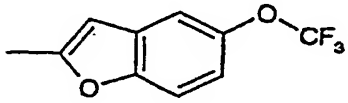
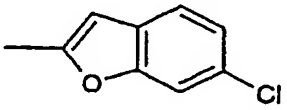
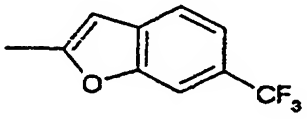
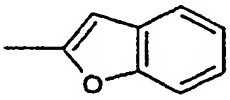
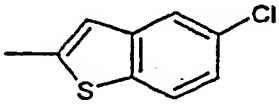
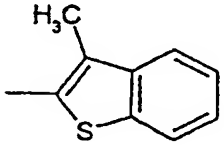
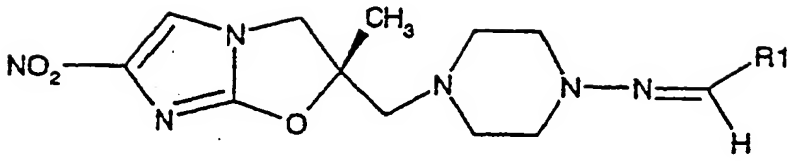
Example	R1	mp(°C)
1255		211.5 - 213.6
1256		190.2 - 191.8
1257		182 - 185.7
1258		192.3 - 195.5
1259		218.4 - 218.9
1260		196 - 197.8
1261		212.5 - 212.9
1262		219.2 - 220
1263		209.4 - 210.4

Table 62



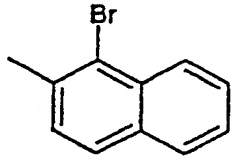
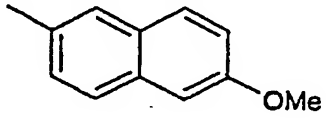
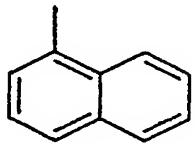
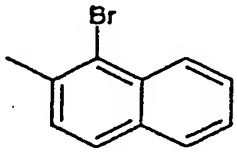
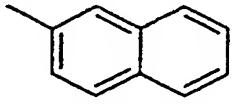
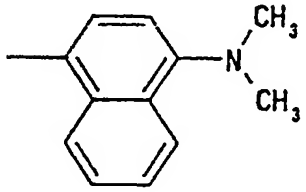
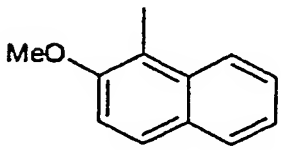
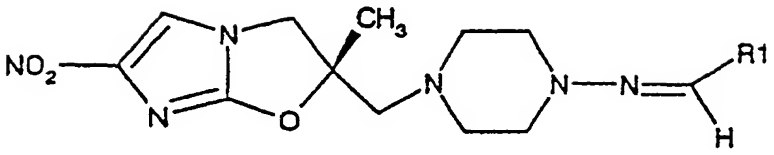
Example	R1	mp(°C) or MS
1264		205.4 - 206.6
1265		214.7 - 215.2
1266		420
1267		498
1268		420
1269		463
1270		450

Table 63



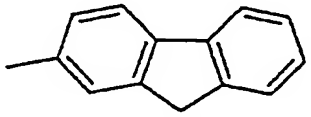
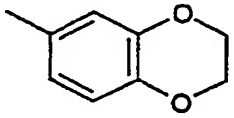
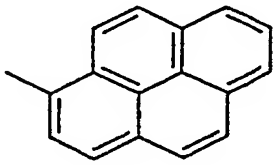
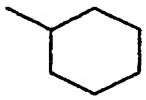
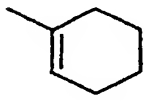
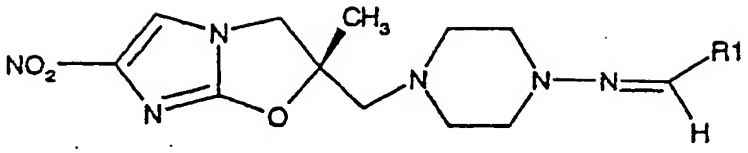
Example	R1	mp(°C) or MS
1271		227.6 - 228.3
1272		428
1273		494
1274		376
1275		374

Table 64



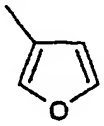
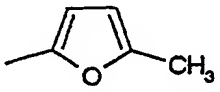
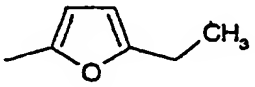
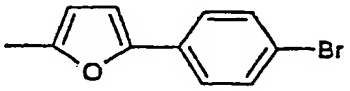
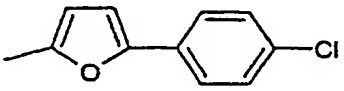
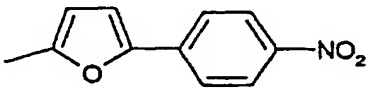
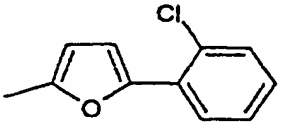
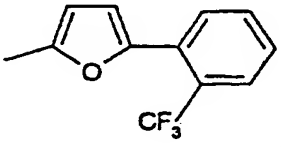
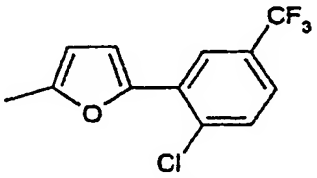
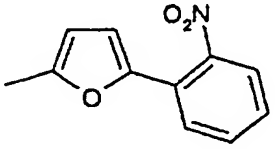
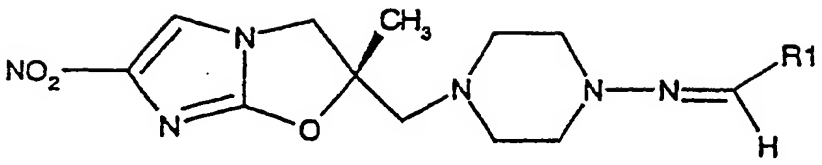
Example	R1	mp(℃) or MS
1276		360
1277		374
1278		388
1279		230.6 - 232.6
1280		470
1281		481
1282		470
1283		504
1284		538
1285		481

Table 65



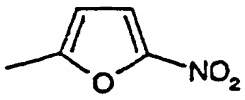
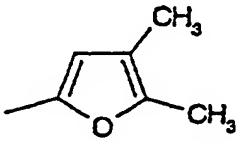
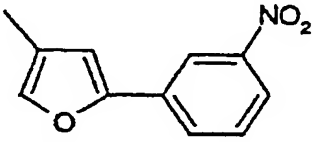
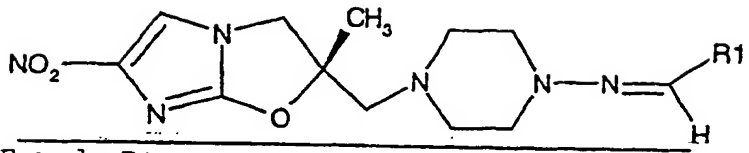
Example	R1	mp(°C) or MS
1286		405
1287		388
1288		481

Table 66



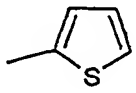
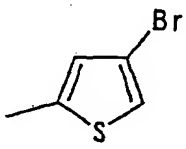
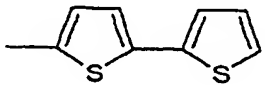
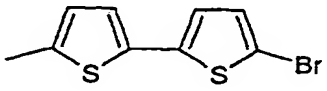
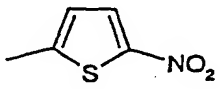
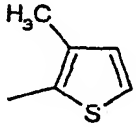
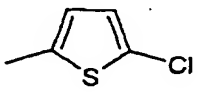
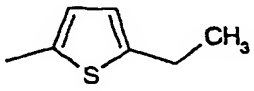
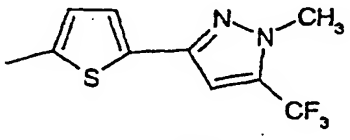
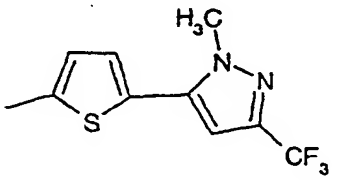
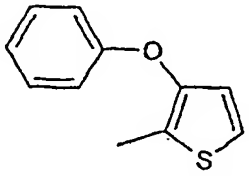
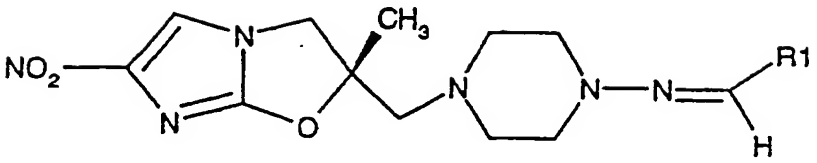
Example	R1	mp(°C) or MS
1289		376
1290		217.8 - 218.5
1291		213.2 - 215.6
1292		536
1293		421
1294		390
1295		410
1296		404
1297		524
1298		524
1299		468

Table 67



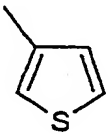
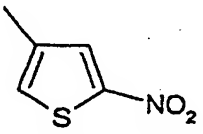
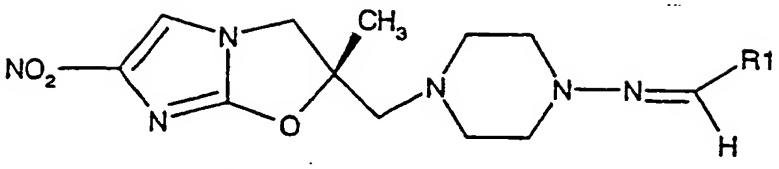
Example	R1	mp(℃) or MS
1300		376
1301		421

Table 68



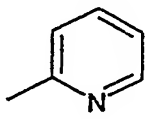
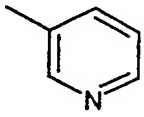
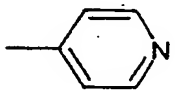
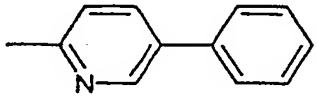
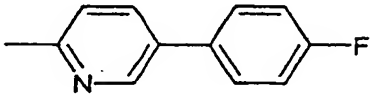
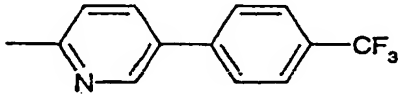
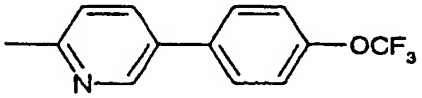
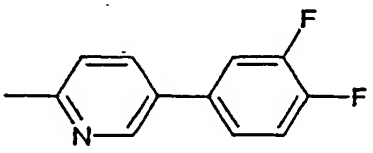
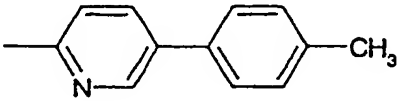
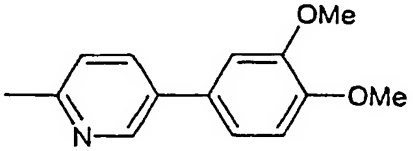
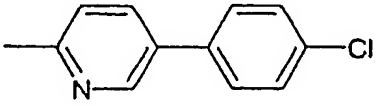
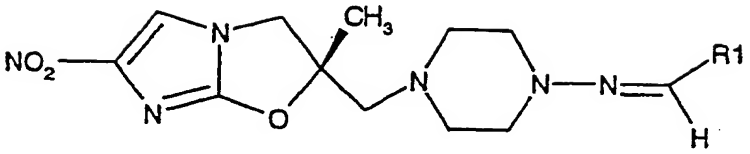
Example	R1	mp(℃) or MS
1302		371
1303		371
1304		371
1305		447
1306		465
1307		515
1308		531
1309		483
1310		461
1311		507
1312		481

Table 69



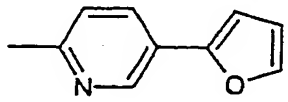
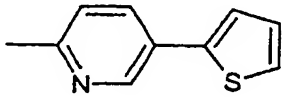
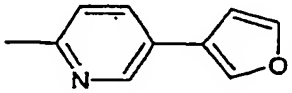
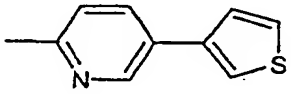
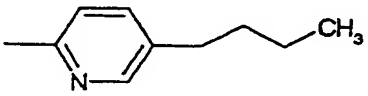
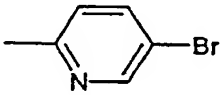
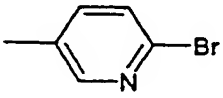
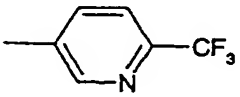
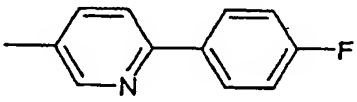
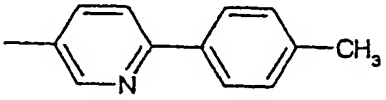
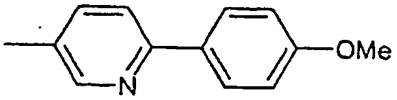
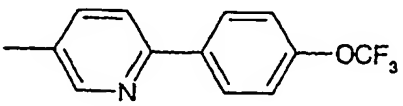
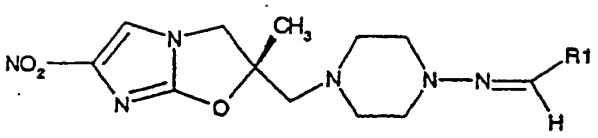
Example	R1	mp(℃) or MS
1313		437
1314		453
1315		437
1316		453
1317		427
1318		449
1319		449
1320		439
1321		465
1322		461
1323		477
1324		531

Table 70



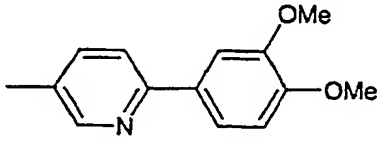
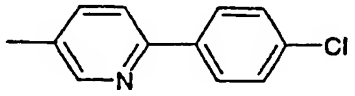
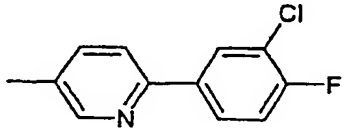
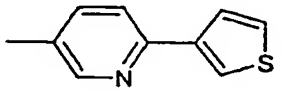
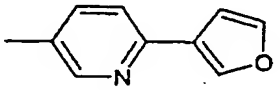
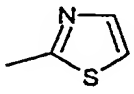
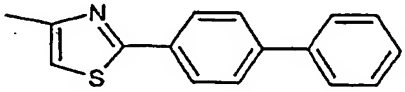
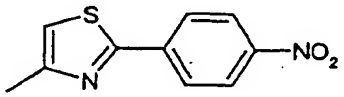
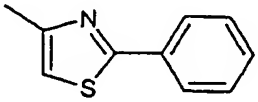
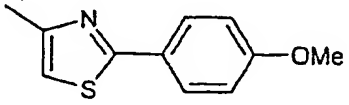
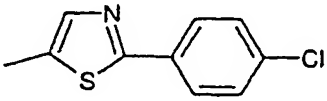
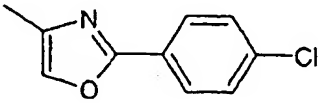
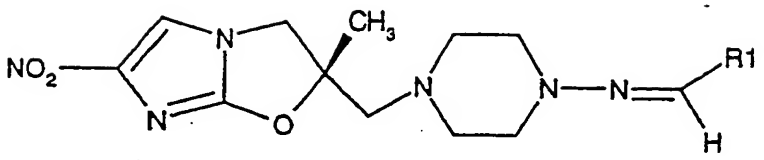
Example	R1	mp(℃) or MS
1325		507
1326		481
1327		499
1328		453
1329		437
1330		377
1331		189.4 - 190.6
1332		498
1333		453
1334		483
1335		487
1336		201.2 - 203.5

Table 71



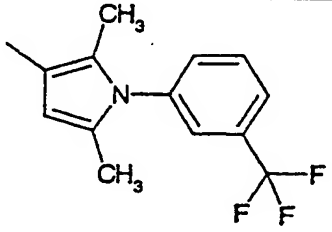
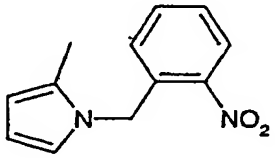
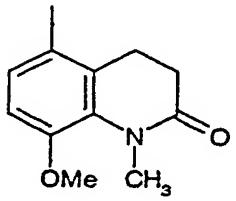
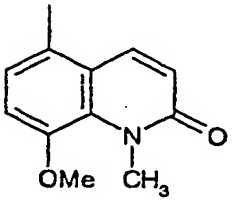
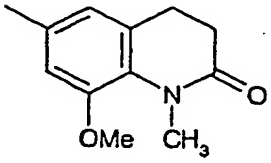
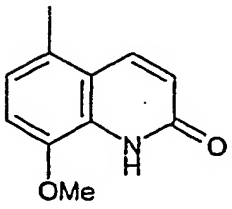
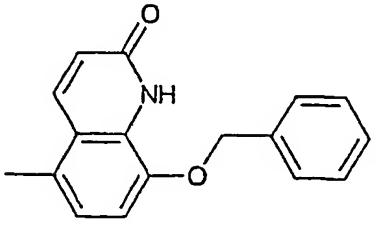
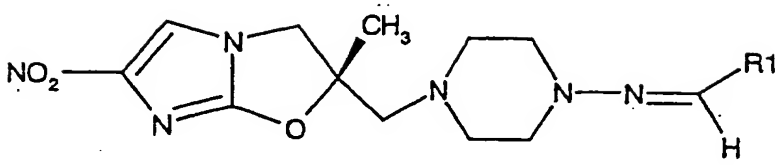
Example	R1	mp(℃) or MS
1337		531
1338		494
1339		483
1340		481
1341		469
1342		467
1343		543

Table 72



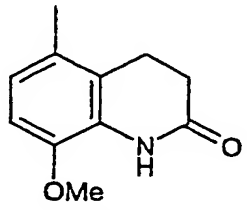
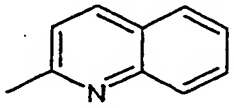
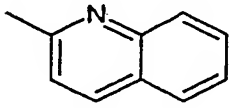
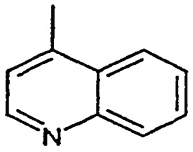
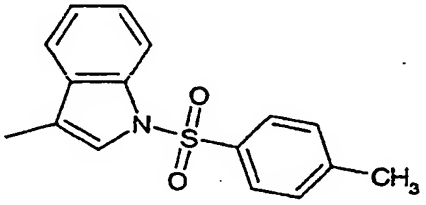
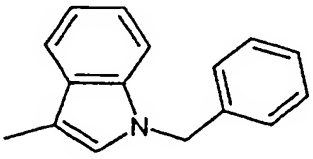
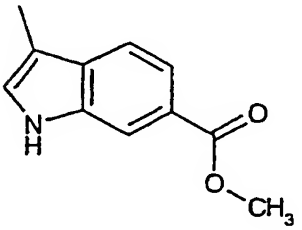
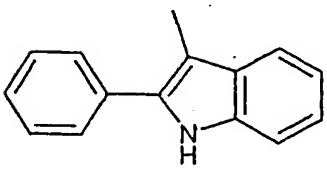
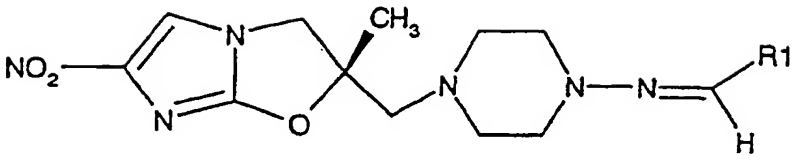
Example	R1	mp(℃) or MS
1344		469
1345		220.6 - 220.9
1346		421
1347		421
1348		563
1349		499
1350		467
1351		485

Table 73



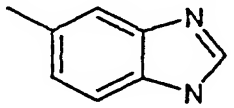
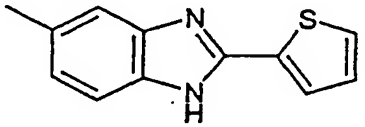
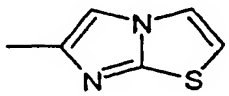
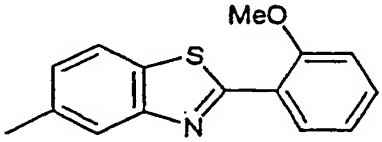
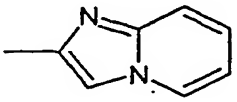
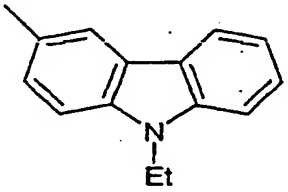
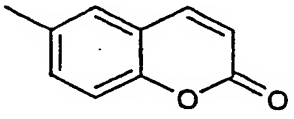
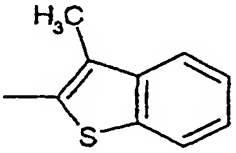
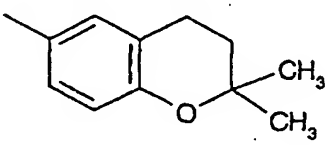
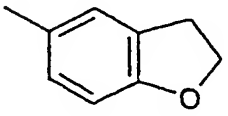
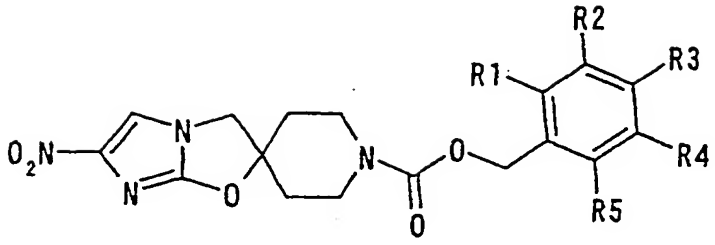
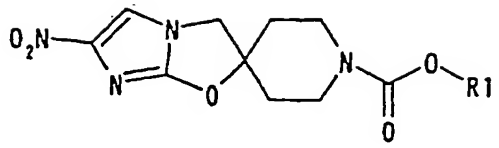
Example	R1	mp(℃) or MS
1352		153.1 - 157.5
1353		492
1354		416
1355		533
1356		410
1357		487
1358		188.6 - 190.6
1359		440
1360		454
1361		412

Table 74



Example	R1	R2	R3	R4	R5	mp(°C)
1362	-H	-H	-F	-H	-H	187 - 188
1363	-H	-H	-Cl	-H	-H	183 - 184
1364	-H	$-OCH_3$	$-OCH_3$	$-OCH_3$	-H	169 - 170
1365	-H	-Cl	-Cl	-H	-H	174 - 175
1366	-Cl	-H	-H	-H	-Cl	208 - 209
1367	-F	-F	-H	-H	-H	184 - 185
1368	-H	-F	-F	-H	-H	185 - 186
1369	-H	-H	$-CO_2CH_3$	-H	-H	183 - 184.5
1370	-H	$-CO_2C_2H_5$	-H	$-CO_2C_2H_5$	-H	181 - 182
1371	-H	-H	$-OCH_3$	-H	-H	175 - 176
1372	-Cl	-H	-H	-H	-H	173 - 174.5
1373	-H	-Cl	-H	-H	-H	173 - 174
1374	-H	$-CF_3$	-H	-H	-H	184 - 186
1375	$-CF_3$	-H	-H	-H	-H	188 - 190
1376	-H	-H	-Ph	-H	-H	187 - 188
1377	-H	$-CF_3$	-H	$-CF_3$	-H	183 - 184
1378	-F	-F	-F	-F	-F	235 - 237
1379	-H	-H	$-SCH_3$	-H	-H	177 - 179
1380	-H	-H	$-C(CH_3)_3$	-H	-H	201 - 202
1381	$-CH_3$	-H	-H	-H	-H	183 - 185
1382	$-OCF_3$	-H	-H	-H	-H	190 - 191
1383	-H	$-OCF_3$	-H	-H	-H	188 - 189

Table 75



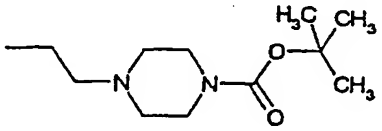
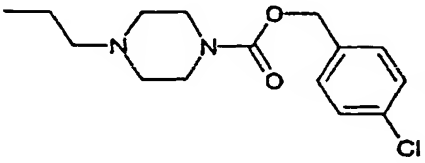
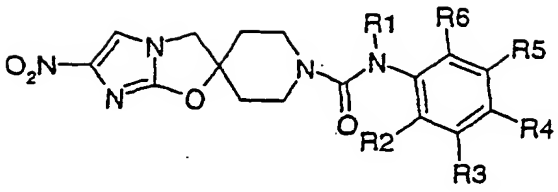
Example	R1	mp(°C)
1384	$(CH_3)_2CH$-	251-253
1385	$(CH_3)_2CHCH_2$-	233-235
1386	C_8H_{17}-	219-220
1387	$Ph(CH_2)_2$-	198-200
1388	$PhCH=CHCH_2$-	180-181
1389	$Ph(CH_2)_3$-	186-187.5
1390	$(Ph)_2CH$-	202-204
1391	Ph-	242-244
1392	2-NaphthylCH_2-	173.5-174.5
1393	4-PyridylCH_2-	163-164
1394	4-Cl$Ph(CH_2)_2$-	198-200
1395	$(4\text{-ClPh})_2CH$-	238-240
1396	4-CH_3Ph-	230-231
1397	4-CH_3OPh-	248-250
1398	2-BocNHPhCH_2-	144-145
1399	$CH_3OCH_2CH_2$-	1.80-2.00 (m, 2H), 2.15-2.25 (m, 2H), 3.30-3.40 (m, 5H), 3.68 (t, 2H, J = 4.5Hz), 3.95-4.20 (m, 4H), 4.27 (t, 2H, J = 4.5Hz), 7.54 (s, 1H)
1400		1.46 (s, 9H), 1.80-1.95 (m, 2H), 2.05-2.15 (m, 2H), 2.40-2.50 (m, 4H), 2.66 (t, 2H, J = 5Hz), 3.25-3.45 (m, 6H), 3.90-4.10(m, 4H), 4.24 (t, 2H, J = 5Hz), 7.54 (s, 1H)
1401		1.80-1.95 (m, 2H), 2.05-2.25 (m, 2H), 2.35-2.60 (m, 4H), 2.63-2.81 (m, 2H), 3.25-3.55 (m, 6H), 3.85-4.25 (m, 6H), 5.09 (s, 2H), 7.20-7.40 (m, 4H), 7.54 (s, 1H)

Table 76



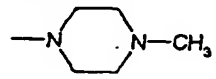
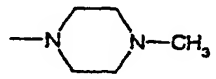
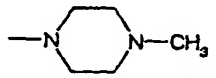
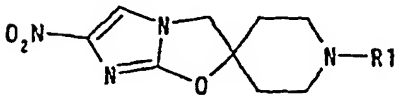
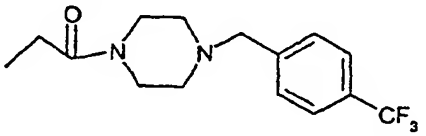
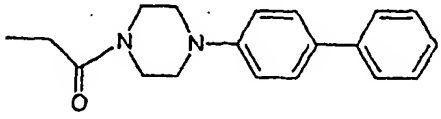
Example	R1	R2	R3	R4	R5	R6	mp(°C)
1402	-H	-H	-H	-Cl	-H	-H	249 - 252(dec.)
1403	-H	-H	-H	-F	-H	-H	238 - 240(dec.)
1404	-H	-H	-H	$-CF_3$	-H	-H	215 - 217
1405	-H	-H	-H	$-OCF_3$	-H	-H	231 - 233
1406	-H	-H	-H	$-CH_3$	-H	-H	>300
1407	-H	-H	-F	Morpholino-	-H	-H	240 - 245(dec.)
1408	-H	-H	-H	$-CO_2C(CH_3)_3$	-H	-H	>300
1409	-H	-H	-Cl		-H	-H	205 - 207
1410	-H	-H	-H		-H	-H	246 - 250(dec.)
1411	-H	-H	-F		-H	-H	220 - 225(dec.)

Table 77



Example	R1	Mp(°C)
1412	PhCO-	178-180
1413	$PhCH_2CO$-	170-171
1414	$Ph(CH_2)_2CO$-	160.5-162
1415	$PhOCH_2CO$-	203-205
1416	$(CH_3)_2CHCH_2CO$-	214-215
1417	4-CF_3PhCO-	165-166
1418	$PhCH_2$-	249-251(dec.)
1419	4-$PhPhCH_2$-	262-264(dec.)
1420		195-197(dec.)
1421		226-227(dec.)

Example 1422

Production of (S)-1-(2-bromo-4-nitroimidazol-1-yl)-2-methyl-3-{4-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]piperazin-1-yl}propan-2-ol

A mixture of (R)-2-bromo-4-nitro-1-(2-methyl-2-oxiranylmethyl)imidazole (485 mg, 1.75 mmol), 1-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]piperazine (720 mg, 2.19 mmol) and ethanol (10 ml) was stirred at 50°C for 8 hours. The reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 20/1) to obtain (S)-1-(2-bromo-4-nitroimidazol-1-yl)-2-methyl-3-{4-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]piperazin-1-yl}propan-2-ol (792 mg, yield 77%)as a yellow amorphous form.

^{1}H-NMR($CDCl_3$) δppm:

1.13(3H, s), 1.50-1.75(2H, m), 1.81-2.00(2H, m), 2.35(1H, d, J = 13.9 Hz), 2.40-2.86(12H, m), 3.57-3.76(2H, m), 3.98(2H, s), 6.89(2H, d, J = 8.5 Hz), 7.09(2H, d, J = 8.5 Hz), 8.12(1H, s).

Following compounds were produced in the same manner.

Example 1423

Tert-butyl (S)-4-{4-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-yl}piperidine-1-carboxylate

^{1}H-NMR($CDCl_3$) δppm:

1.12(3H, s), 1.29-1.48(11H, m), 1.67-1.81(2H, m),

2.34(1H, d, J = 13.8 Hz), 2.38-2.74(12H, m), 3.97(2H, s), 4.02-4.14(2H, m), 8.05(1H, s).

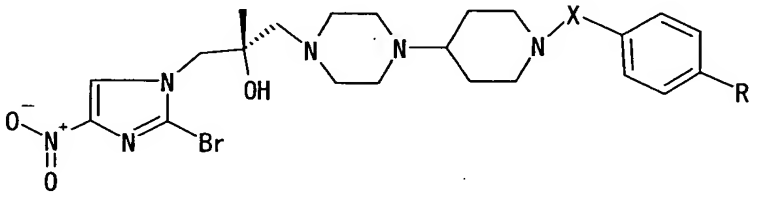
Example 1424

Tert-butyl (S)-4-{1-[3-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperidin-4-yl}piperazin-1-carboxylate

^{1}H-NMR($CDCl_3$) δppm:

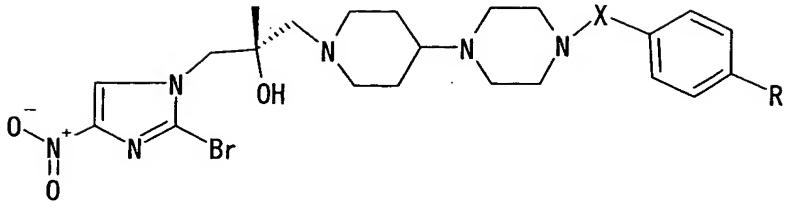
1.11(3H, s), 1.38-1.57(11H, m), 1.69-1.86(2H, m), 2.24-2.50(9H, m), 2.67-2.79(1H, m), 2.86-3.00(1H, m), 3.31-3.43(4H, m), 3.95(2H, s), 8.04(1H, s).

Table 78



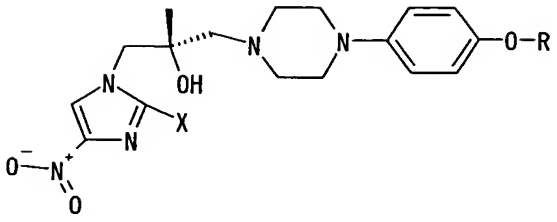
Example	X	R	^{1}H-NMR ($CDCl_3$) δppm
1425	none	OCF_3	1.13(3H, s), 1.50-1.75(2H, m), 1.81-2.00(2H, m), 2.35(1H, d, J=13.9Hz), 2.40-2.86(12H, m), 3.57-3.76(2H, m), 3.98(2H, s), 6.89(2H, d, J=8.5Hz), 7.09(2H, d, J=8.5Hz), 8.12(1H, s).
1426	C=O	Cl	1.13(3H, s), 1.31-1.56(2H, m), 1.70-2.00(2H, m), 2.36(1H, d, J=13.9Hz), 2.65-2.91(12H, m), 3.63-3.84(1H, m), 3.93(2H, s), 4.56-4.74(1H, m), 7.19-7.42(4H, m), 8.13(1H, s).
1427	C=O	OCF_3	1.14(3H, s), 1.35-1.60(2H, m), 1.74-2.00(2H, m), 2.36(1H, d, J=13.9Hz), 2.42-2.93(12H, m), 3.65-3.81(1H, m), 4.00(2H, s), 4.56-4.74(1H, m), 7.25(2H, d, J=8.7Hz), 7.44(2H, d, J=8.7Hz), 8.14(1H, s).
1428	CH_2	Cl	1.12(3H, s), 1.43-2.05(6H, m), 2.34(1H, d, J=13.9Hz), 2.37-2.95(12H, m), 3.47(2H, s), 3.97(2H, s), 7.12-7.30(4H, m), 8.12(1H, s).
1429	CH_2	OCF_3	1.12(3H, s), 1.44-2.05(6H, m), 2.35(1H, d, J=14.0Hz), 2.42-2.93(12H, m), 3.48(2H, s), 3.98(2H, s), 7.15(2H, d, J=8.6Hz), 7.34(2H, d, J=8.6Hz), 8.12(1H, s).

Table 79



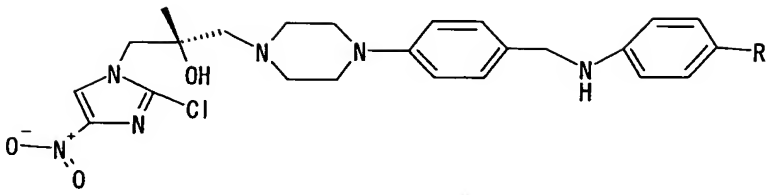
Example	X	R	^{1}H-NMR ($CDCl_3$) δppm
1430	C=O	Cl	1.12(3H, s), 1.43-1.81(4H, m), 2.10-2.62(9H, m), 2.71-3.07(2H, m), 3.31-3.45(4H, m), 3.96(2H, s), 7.24-7.40(4H, m), 8.10(1H, s).
1431	C=O	OCF_3	1.12(3H, s), 1.45-1.83(4H, m), 2.12-2.57(9H, m), 2.71-3.07(2H, m), 3.28-3.47(4H, m), 3.96(2H, s), 7.25(2H, d, J=8.6Hz), 7.45(2H, d, J=8.6Hz), 8.10(1H, s).
1432	CH_2	OCF_3	1.11(3H, s), 1.50-1.98(4H, m), 2.24-3.10(15H, m), 3.54(2H, s), 3.98(2H, s), 7.16(2H, d, J=8.6Hz), 7.34(2H, d, J=8.6Hz), 8.12(1H, s).
1433	CH_2	Cl	1.11(3H, s), 1.40-1.83(4H, m), 2.25-3.02(15H, m), 3.46(2H, s), 3.95(2H, s), 7.14-7.29(4H, m), 8.12(1H, s).
1434	none	OCF_3	1.13(3H, s), 1.50-1.64(2H, m), 1,76-1.88(2H, m), 2.15-2.43(5H, m), 2.52-2.95(6H, m), 3.05-3.19(4H, m), 3.98(2H, s), 6.89(2H, d, J=8.7Hz), 7.11(2H, d, J=8.7Hz), 8.1 (1H, s).
1435	none	Cl	1.13(3H, s), 1.50-1.64(2H, m), 1,71-1.90(2H, m), 2.12-2.48(5H, m), 2.55-2.90(6H, m), 3.05-3.19(4H, m), 3.96(2H, s), 6.84(2H, d, J=8.7Hz), 7.18(2H, d, J=8.7Hz), 8.11(1H, s).

Table 80



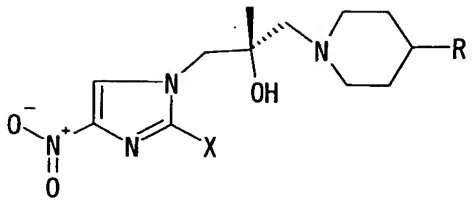
Example	X	R	^{1}H-NMR ($CDCl_3$) δppm
1436	Cl	4-ClPh-	1.17(3H, s), 2.41(1H, d, J=13.9Hz), 2.56(1H, d, J=13.9Hz), 2.63-2.73(2H, m), 2.76-2.92(2H, m), 3.08-3.18(4H, m), 3.40(1H, s), 4.01(2H, s), 6.80-6.96(6H, m), 7.14-7.24(2H, m), 8.06(1H, s).
1437	Br	4-CF_3PhCH_2-	1.16(3H, s), 2.39(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.65-2.78(2H, m), 2.84-2.92(2H, m), 3.02-3.14(4H, m), 3.46(1H, s), 4.01(2H, s), 5.08(2H, s), 6.89(4H, m), 7.48(2H, d, J=8.3Hz), 7.63(2H, d, J=8.3Hz), 8.12(1H, s).
1438	Br	4-$ClPhCH_2$-	1.16(3H, s), 2.39(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.63-2.78(2H, m), 2.80-2.96(2H, m), 3.04-3.12(4H, m), 3.47(1H, s), 4.01(2H, s), 4.98(2H, s), 6.88(4H, s), 7.35(4H, s), 8.12(1H, s).
1439	Cl	4-CF_3OPhCH_2-	1.16(3H, s), 2.40(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.65-2.76(2H, m), 2.78-2.92(2H, m), 3.04-3.12(4H, m), 3.45(1H, s), 4.00(2H, s), 5.0 (2H, s), 6.89(4H, s), 7.22(2H, d, J=8.6Hz), 7.45(2H, d, J=8.6Hz), 8.06 (1H, s).
1440	Cl	4-CF_3OPh-	1.18(3H, s), 2.41(1H, d, J=13.9Hz), 2.56(1H, d, J=13.9Hz), 2.65-2.76(2H, m), 2.78-2.88(2H, m), 3.06-3.20(4H, m), 3.39(1H, s), 4.02(2H, s), 6.84-7.00(6H, m), 7.14(2H, d, J=8.3Hz), 8.06(1H, s).
1441	Cl	4-CF_3Ph-	1.18(3H, s), 2.42(1H, d, J=13.9Hz), 2.57(1H, d, J=13.9Hz), 2.65-2.77(2H, m), 2.79-2.92(2H, m), 3.06-3.20(4H, m), 3.40(1H, s), 4.03(2H, s), 6.80-7.00(6H, m), 7.53(2H, d, J=8.6Hz), 8.07(1H, s).

Table 81



Example	R	^{1}H-NMR ($CDCl_3$) δppm
1442	Cl-	1.17(3H, s), 2.40(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.65-2.92(4H, m), 3.08-3.24(4H, m), 3.40(2H, s), 4.00(2H, s), 4.20(2H, s), 6.54(2H, d, J=8.7Hz), 6.88(2H, d, J=8.7Hz), 7.09(2H, d, J=8.7Hz), 7.18-7.25(2H, m), 8.06(1H, s).
1443	CF_3O-	1.16(3H, s), 2.41(1H, d, J=13.9Hz), 2.55(1H, d, J=13.9Hz), 2.65-2.92(4H, m), 3.08-3.25(4H, m), 3.44(2H, s), 4.02(2H, s), 4.21(2H, s), 6.57(2H, d, J=8.6Hz), 6.89(2H, d, J=8.6Hz), 7.01(2H, d, J=8.3Hz), 7.22(2H, d, J=8.3Hz), 8.06(1H, s).

Table 82



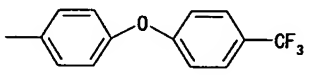
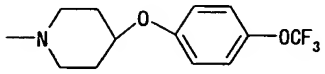
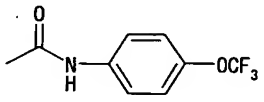
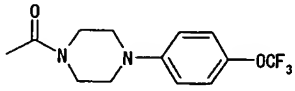
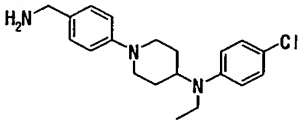
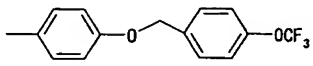
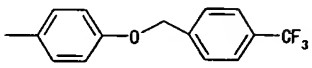
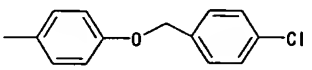
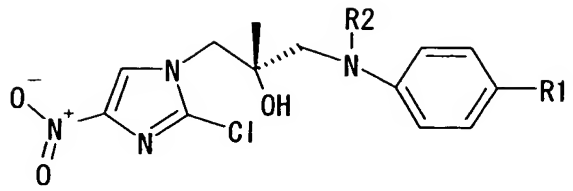
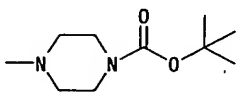
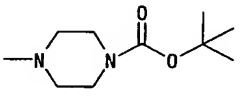
Example	X	R	^{1}H-NMR ($CDCl_3$) δppm
1444	Cl		1.15(3H, s), 1.51-1.86(4H, m), 2.27-2.57(3H, m), 2.75-2.92(2H, m), 3.00-3.16(2H, m), 3.56(1H, s), 4.17(2H, s), 6.90-7.02(4H, m), 7.10-7.25(2H, m), 7.56(2H, d, J=8.8Hz), 8.01(1H, s).
1445	Br		1.25(3H, s), 1.50-2.00(8H, m), 2.24-2.67(7H, m), 2.75-3.20(4H, m), 3.97(2H, s), 4.25-4.40(1H, m), 6.88(2H, d, J=8.8Hz), 7.13(2H, d, J=8.8Hz), 8.12(1H, s).
1446	Cl		1.14(3H, s), 1.76-1.93(4H, m), 2.24-2.52(5H, m), 2.74-2.86(1H, m), 2.95-3.07(1H, m), 3.98(2H, s), 7.17(2H, d, J=8.8Hz), 7.55(2H, d, J=8.8Hz), 8.05(1H, s).
1447	Cl		1.13(3H, s), 1.51-1.90(4H, m), 2.19-2.55(5H, m), 2.71-2.83(1H, m), 2.85-3.19(5H, m), 3.51-3.83(4H, m), 3.98(2H, s), 6.90(2H, d, J=8.3Hz), 7.13(2H, d, J=8.3Hz), 8.05(1H, s).
1448	Cl		1.15(3H, s), 1.39-1.83(5H, m), 2.33-2.62(3H, m), 3.00-3.15(2H, m), 3.49-3.61(2H, m), 4.17(2H, s), 6.97-7.05(4H, m), 7.21-7.24(2H, m), 7.53-7.58(2H, m), 8.08(1H, s)
1449	Cl		1.14(3H, s), 1.61-1.81(5H, m), 2.34-2.57(3H, m), 2.77-2.84(2H, m), 3.01-3.06(2H, m), 3.99(2H, s), 5.04(2H, s), 6.89-6.95(2H, m), 7.11-7.25(4H, m), 7.43-7.48(2H, m), 8.09(1H, s)
1450	Cl		1.14(3H, s), 1.45-1.80(5H, m), 2.38-2.60(3H, m), 2.78-2.90(2H, m), 3.01-3.06(2H, m), 3.98(2H, s), 5.11(2H, s), 6.89-6.93(2H, m), 7.12-7.18(2H, m), 7.52-7.55(2H, m), 7.62-7.65(2H, m), 8.08(1H, s)
1451	Cl		1.14(3H, s), 1.38-1.80(5H, m), 2.28-2.60(3H, m), 2.77-2.93(2H, m), 3.02-3.08(2H, m), 3.98(2H, s), 5.01(2H, s), 6.84-6.92(2H, m), 7.11-7.16(2H, m), 7.32-7.36(4H, m), 8.08(1H, s)

Table 83



Example	R1	R2	^{1}H-NMR ($CDCl_3$) δppm
1452		CH_3	1.13(3H, s), 1.48(9H, s), 2.42(3H, s), 2.43(2H, s), 3.03-3.13(4H, m), 3.42(1H, d, J=10.7Hz), 3.50-3.63(5H, m), 3.85(2H, s), 6.84(2H, d, J=7.1Hz), 7.11(2H, d, J=7.1Hz), 7.88(1H, s).
1453		C_2H_5	1.06-1.11(6H, m), 1.48(9H, s), 2.41(1H, d, J=13.2Hz), 2.55(1H, d, J=13.2Hz), 2.64-2.68(2H, m), 3.10-3.13(4H, m), 3.42(1H, d, J=13.2Hz), 3.57-3.60(4H, m), 3.69(1H, d, J=13.2Hz), 3.79(2H, s), 6.83-6.86(2H, m), 7.09-7.12(2H, m), 7.84(1H, s).

Example 1454

Production of (S)-2-methyl-6-nitro-2-{4-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]piperazin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole

(S)-1-(2-bromo-4-nitroimidazol-1-yl)-2-methyl-3-{4-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]piperazin-1-yl}propan-2-ol (790 mg, 1.34 mmol) was dissolved in N,N-dimethylformamide (4 ml), sodium hydride (69 mg, 1.74 mmol) was added while cooling on ice, and the solution was stirred at the same temperature for 1 hour. To the reaction mixture, ethyl acetate (1.3 ml) and water (10 ml) were added in this order, and the precipitated crystals were filtered off and washed with water. The crystals were purified by

silica gel column chromatography (methylene chloride/methanol = 10/1) and recrystallized from ethyl acetate/isopropyl ether to obtain (S)-2-methyl-6-nitro-2-{4-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]piperazin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole (270 mg, yield 40%) as a white powder.
Melting point 180-181.5°C.

Following compounds were produced in the same manner.

Example 1455

(S)-2-{4-[4-(4-chlorophenyl)piperazin-1-yl]piperidin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 34%

Melting point 226-228°C.

Example 1456

(S)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenyl)piperazin-1-yl]piperidin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole

Yield 23%

Melting point 193-194°C.

Example 1457

(S)-2-{4-[4-(4-chlorobenzyl)piperazin-1-yl]piperidin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 25%

Melting point 148-149°C.

Example 1458

(S)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxy-benzyl)piperazin-1-yl]piperidin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole

Yield 21%

Melting point 142-143°C.

Example 1459

(S)-(4-chlorophenyl)-{4-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]piperazin-1-yl}methanone

Yield 29%

Melting point 174-175°C.

Example 1460

(S)-{4-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]piperazin-1-yl}-(4-trifluoromethoxyphenyl)methanone

Yield 29%

Melting point 137-138°C.

Example 1461

(S)-2-{4-[1-(4-chlorobenzyl)piperidin-4-yl]piperazin-1-ylmethyl}-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Yield 24%

Melting point 168-169°C.

Example 1462

(S)-2-methyl-6-nitro-2-{4-[1-(4-trifluoromethoxy-benzyl)piperidin-4-yl]piperazin-1-ylmethyl}-2,3-dihydroimidazo[2,1-b]oxazole

Yield 27%

Melting point 140-141°C.

Example 1463

(S)-(4-chlorophenyl)-{4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]piperidin-1-yl}methanone

Yield 30%

Melting point 218-220°C.

Example 1464

(S)-{4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]piperidin-1-yl}-(4-trifluoromethoxyphenyl)methanone

Yield 27%

Melting point 133-134°C.

Example 1465

(S)-1'-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-4-(4-trifluoromethoxyphenoxy)-[1,4']bipiperidinyl

Yield 41%

Melting point 131-132°C.

Example 1466

Production of tert-butyl (S)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]piperidine-1-carboxylate

A mixture of (R)-2-chloro-4-nitro-1-(2-methyl-2-oxiranylmethyl)imidazole (3 g, 13.79 mmol), tert-butyl 4-piperazin-1-yl-piperidine-1-carboxylate (3.9 g, 14.48 mmol), and ethanol (30 ml) was stirred at

50°C for 9 hours. The reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 10/1) to obtain a yellow amorphous form. The amorphous form was dissolved in N,N-dimethylformamide (18 ml), sodium hydride (651 mg, 16.28 mmol) was added while cooling on ice, and the resultant solution was stirred at the same temperature for 1 hour. To the reaction mixture, ethyl acetate (6 ml) and water (42 ml) were added in this order, and the precipitated crystals were filtered off and washed with water. The filtrate was recrystallized from 2-propanol (20 ml)/water (60 ml) to obtain tert-butyl (S)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]piperidine-1-carboxylate (4.08 g, 66%) as a light yellow powder.

Melting point 181-182°C.

The following compound was produced in the same manner.

Example 1467

Tert-butyl (S)-4-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]piperazine-1-carboxylate

Yield 56%

Melting point 184-185°C.

Example 1468

Production of 4-trifluoromethoxybenzyl (S)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-

ylmethyl)piperazin-1-yl]piperidine-1-carboxylate

A mixture of 4-(trifluoromethoxy)benzyl alcohol (480 mg, 2.50 mmol), 1,1'-carbonylbis-1H-imidazole (405 mg, 2.50 mmol), and N,N-dimethylformamide (3 ml) was stirred at room temperature for 14 hours.

Meanwhile, tert-butyl (S)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)-piperazin-1-yl]piperidine-1-carboxylate (750 mg, 1.66 mmol) was dissolved in methylene chloride (5 ml), trifluoroacetic acid (5 ml) was added, and the resultant solution was stirred at room temperature for 14 hours. The reaction mixture was concentrated. To the residue, methanol (5 ml) and triethylamine (5 ml) were added, and the mixture was stirred at room temperature for 10 minutes and then concentrated. The residue was dissolved in N,N-dimethylformamide (5 ml). The solution was added to the above described N,N-dimethylformamide solution followed by stirring at 50°C for 3 hours.

The reaction mixture was allowed to return to room temperature, poured in water (40 ml), and extracted with ethyl acetate (30 ml) twice. The organic phases were combined, washed with water (40 ml) twice followed by a saturated saline solution (30 ml), and then dried over sodium sulfate. After filtration, the filtrate was concentrated, and the residue was purified by silica gel column chromatography (methylene

chloride/methanol = 10/1) and then recrystallized from ethyl acetate/isopropyl ether to obtain 4-trifluoromethoxybenzyl (S)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]piperidine-1-carboxylate (545 mg, 58%) as a light brown powder.

Melting point 105-106°C.

The following compound was produced in the same manner.

Example 1469

4-Trifluoromethoxybenzyl (S)-4-[1-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperidin-4-yl]piperazin-1-carboxylate

Yield 64%

Melting point 110-111°C.

Example 1470

Production of (S)-2-methyl-6-nitro-2-[4-{1-[3-(4-trifluoromethoxyphenyl)-2-propenyl]piperidin-4-yl}piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

Tert-butyl (S)-4-[4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazin-1-yl]piperidine-1-carboxylate (750 mg, 1.66 mmol) was dissolved in methylene chloride (5 ml), trifluoroacetic acid (5 ml) was added followed by stirring at room temperature for 1.5 hours. The reaction mixture was concentrated. To the residue, methylene chloride (5 ml) and triethylamine (5 ml) were added, and the

mixture was stirred at room temperature for 10 minutes and then concentrated. The residue was dissolved in 1,2-dichloroethane (20 ml), 3-(4-trifluoromethoxyphenyl)propenal (396 mg, 1.83 mmol) and sodium triacetoxyborohydride (564 mg, 2.66 mmol) were added followed by stirring at room temperature for 3.5 hours. The reaction solution was washed with a saturated sodium hydrogencarbonate solution (15 ml), water (20 ml), and a saturated saline solution (20 ml) in this order, and then dried over sodium sulfate. After filtration, the filtrate was concentrated, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 10/1) and then recrystallized from methanol/water to obtain (S)-2-methyl-6-nitro-2-[4-{1-[3-(4-trifluoromethoxyphenyl)-2-propenyl]piperidin-4-yl}piperazin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole (446 mg, 49%) as a light yellow powder.

Melting point 157-158°C.

Following compounds were produced in the same manner.

Example 1471

(S)-2-methyl-6-nitro-2-[4-{4-[3-(4-trifluoromethoxyphenyl)-2-propenyl]piperazin-1-yl}piperidin-1-ylmethyl]-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 174-175°C.

Example 1472

(S)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxy-

phenoxy)phenyl]piperazin-1-ylmethyl}-2,3-dihydro-imidazo[2,1-b]oxazole 4-toluenesulfonate

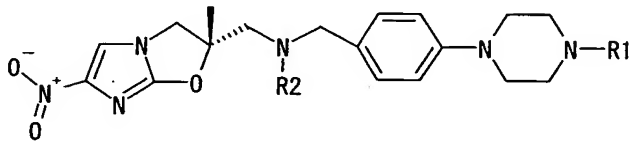
Melting point 146.1-148.6°C.

Example 1473

(S)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxy-phenoxy)phenyl]piperazin-1-ylmethyl}-2,3-dihydro-imidazo[2,1-b]oxazole hydrochloride

Melting point 133-137°C.

Table 84



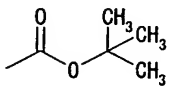
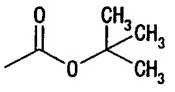
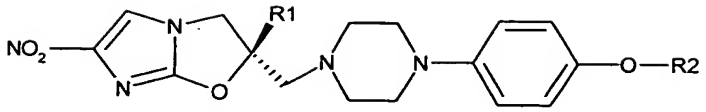
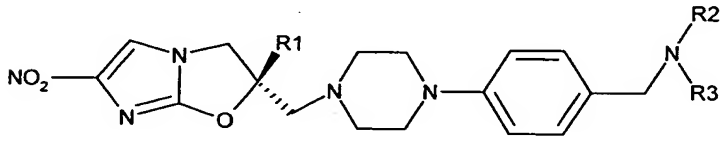
Example	R1	R2	^{1}H-NMR ($CDCl_3$) δppm
1474		CH_3	1.48(9H, s), 1.55(3H, s), 2.36(3H, s), 2.61(1H, d, J=12.3Hz), 2.80(1H, d, J=12.3Hz), 3.03-3.15(4H, m), 3.41(1H, d, J=10.8Hz), 3.48-3.60(5H, m), 3.69 (1H, d, J=8.1Hz), 4.08 (1H, d, J=8.1Hz), 6.85 (2H, d, J=7.1Hz), 7.06 (2H, d, J=7.1Hz), 7.46 (1H, s).
1475		C_2H_5	0.97(3H, t, J=7.1Hz), 1.49(9H, s), 1.53(3H, s), 2.54-2.78(3H, m), 2.93-2.96(1H, m), 3.10-3.13(4H, m), 3.39-3.43(1H, m), 3.57-3.67(6H, m), 3.96(1H, d, J=9.8Hz), 6.83-6.85(2H, m), 7.02-7.05(2H, m), 7.43(1H, s).
1476	H	CH_3	1.53(3H, s), 2.37(3H, s), 2.60(1H, d, J=12.2Hz), 2.78(1H, d, J=12.2Hz), 2.98-3.18(8H, m), 3.40(1H, d, J=10.8Hz), 3.55(1H, d, J=10.8Hz), 3.66(1H, d, J=8.1Hz), 4.04(1H, d, J=8.1Hz), 6.85(2H, d, J=7.1Hz), 7.06(2H, d, J=7.1Hz), 7.45(1H, s).
1477	H	C_2H_5	0.98(3H, t, J=7.1Hz), 1.53(3H, s), 2.55-2.75(3H, m), 2.93-2.95(1H, m), 3.15-3.18(4H, m), 3.24-3.28(4H, m), 3.37-3.43(1H, m), 3.62-3.67(2H, m), 3.94(1H, d, J=9.8Hz), 6.82-6.87(2H, m), 7.02-7.05(2H, m), 7.44(1H, s).

Table 85



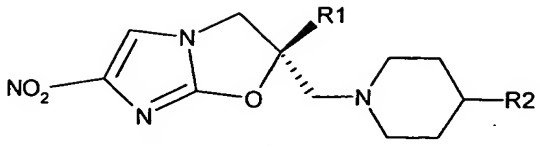
Example	R1	R2	mp(°C)
1478	$-CH_3$	4-ClPh-	202.6 - 204.0 dec
1479	$-CH_3$	$4-CF_3PhCH_2-$	172.0 - 174.2
1480	$-CH_3$	$4-ClPhCH_2-$	227.0 - 228.3 dec
1481	$-CH_3$	$4-CF_3OPhCH_2-$	176 - 179.5
1482	$-CH_3$	$4-CF_3OPh-$	114.1 - 116.6
1483	$-CH_3$	$4-CF_3Ph-$	105 - 110

Table 86



Example	R1	R2	R3	mp(°C)
1484	$-CH_3$	$-CH_3$	4-ClPh-	126.2-127.5
1485	$-CH_3$	$-CH_3$	$4-CF_3OPh-$	103.0-106.6
1486	$-CH_3$	-H	4-ClPh-	209.8 - 210.3 dec
1487	$-CH_3$	-H	$4-CF_3OPh-$	110.0 - 113.5

Table 87



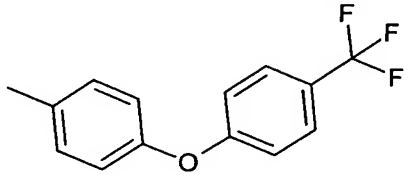
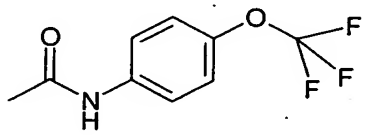
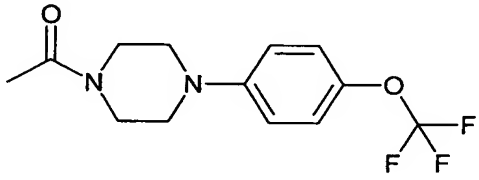
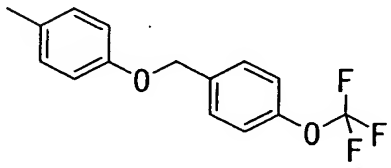
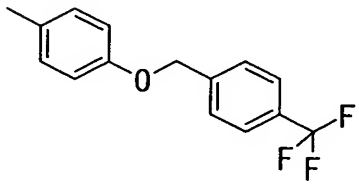
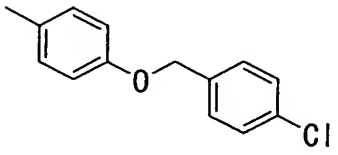
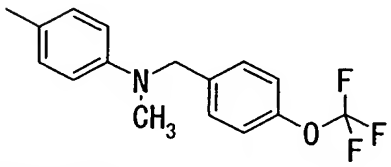
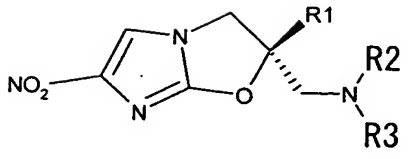
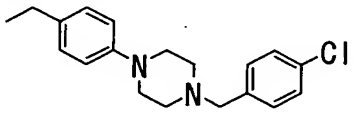
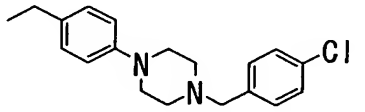
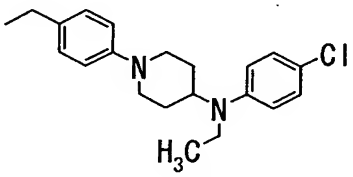
Example	R1	R2	mp (°C) or ^{1}H NMR
1488	$-CH_3$		110.6-111.7
1489	$-CH_3$		^{1}H NMR($CDCl_3$) δppm 1.56-1.71 (7H, m), 2.16(3H, m), 2.57(1H, d, J=14.9Hz), 2.76-3.10(3H, m), 3.93(1H, d, J=9.8Hz), 4.36(1H, d, J=9.8Hz), 7.12(2H, d, J=8.5Hz), 7.55-7.68(3H, m), 9.04(1H, s).
1490	$-CH_3$		^{1}H NMR($CDCl_3$) δppm 1.48-1.68 (4H, m), 1.75-1.95(1H, m), 2.19-2.56(4H, m), 2.75-3.19 (9H, m), 3.53-3.77(4H, m), 3.88(1H, d, J=9.7Hz), 4.36(1H, d, J=9.7Hz), 6.89(2H, d, J=8.5Hz), 7.13(2H, d, J=8.5Hz), 7.68(1H, s).
1491	$-CH_3$		148.4 - 149.7
1492	$-CH_3$		160.4 - 161.8
1493	$-CH_3$		164.4 - 167.3 dec
1494	$-CH_3$		140.2 - 142.8

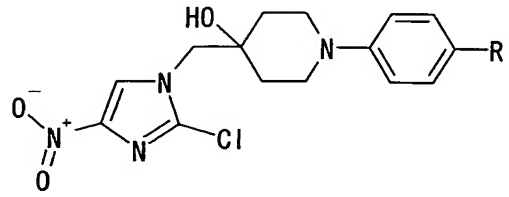
Table 88

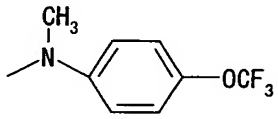
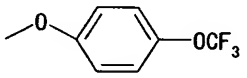
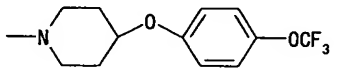
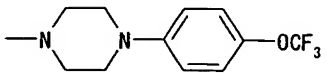


Example	R1	R2	R3	mp(°C) or ^{1}H NMR
1495	$-CH_3$		$-CH_3$	143.1 - 145.8
1496	$-CH_3$		$-C_2H_5$	^{1}H NMR($CDCl_3$) δ 0.97(3H, t, J=7.1Hz), 1.51(3H, s), 2.58-2.76(7H, m), 2.89(1H, d, J=14.9Hz), 3.17-3.20(4H, m), 3.38(1H, d, J=13.3Hz), 3.54-3.64(4H, m), 3.89(1H, d, J=9.8Hz), 6.82-6.85(2H, m), 7.01-7.04(2H, m), 7.27-7.30(4H, m), 7.41(1H, s).
1497	$-CH_3$		$-CH_3$	100.7 - 103.0

The following compounds were produced in the same manner as in Example 649.

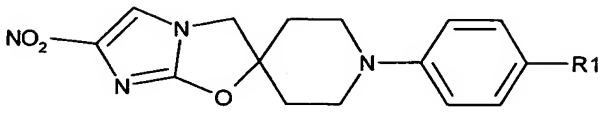
Table 89

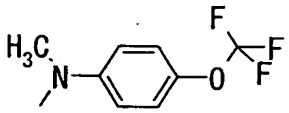
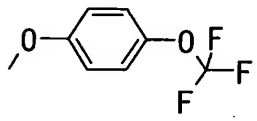
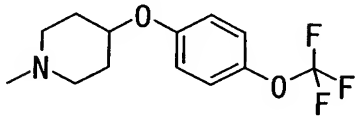
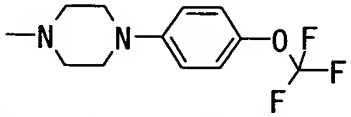


Example	R	Solvent	^{1}H-NMR δppm
1498	-Cl	DMSO-d_6	1.32-1.50(2H,m),1.55-1.75(2H,m), 2.86-3.02(2H, m),3.36-3.50 (2H,m),4.05(2H,s),4.93(1H,s),6.95(2H,d,J=8.9Hz),7.21(2H,d,J=8.9Hz), 8.35(1H, s).
1499	-OCF_3	DMSO-d_6	1.51-1.67(2H,m),1.76-1.94(2H,m), 2.02(1H,s),2.96-3.12(2H,m),3.37-3.56(2H,m),4.07(2H,s),6.9(2H,d,J=8.9Hz),7.12(2H,d,J=8.9Hz),8.00 (1H,s).
1500		$CDCl_3$	1.57-1.71(2H,m),1.78-1.98(2H,m), 2.92-3.08(2H,m),3.24(3H,s),3.35-3.51(2H,m),4.09(2H,s),6.74(2H,d, J=8.9Hz),6.88-7.10(6H,m), 8.02(1H,s).
1501		$CDCl_3$	1.55-1.69(2H,m),1.80-1.98(2H,m), 2.92-3.08(2H,m),3.33-3.49(2H,m), 4.09(2H,s),6.82-6.98(6H,m),7.14 (2H,d,J=8.9Hz),8.02(1H,s).
1502		$CDCl_3$	1.53-1.67(2H,m),1.80-2.16(6H,m), 2.84-3.06(4H,m),3.24-3.45(4H,m), 4.11(2H,s),4.33-4.47(1H,m),6.80-6.92(6H,m),7.14(2H,d,J=8.9Hz), 8.00(1H, s).
1503		$CDCl_3$	1.53-1.65(2H,m),1.82-1.98(2H,m), 2.84-3.00(2H,m),3.14-3.39 (10H,m),4.07(2H,s),6.84-6.96 (6H,m),7.14(2H,d,J=8.6Hz),8.01 (1H,s).

The following compounds were produced in the same manner as in Example 652.

Table 90



Example	R1	mp (°C)
1504	-Cl	242.0 - 245.0
1505	$-OCF_3$	235.9 - 236.8dec.
1506		214.0 - 215.1dec.
1507		227.3-229.4
1508		237.6-238.4
1509		254.2 - 256.8

The following compounds were produced in the same manner as in Example 128.

Example 1510

(R)-2-methyl-6-nitro-2-{4-[1-(4-trifluoromethoxy-benzyl)piperidin-4-yl]phenoxymethyl}-2,3-dihydro-imidazo[2,1-b]oxazole

Melting point 186-188°C.

Example 1511

(R)-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)-piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-

b]oxazole

Melting point 157-160°C.

Example 1512

(R)-2-methyl-6-nitro-2-{4-[3-(4-trifluoromethoxy-phenoxy)-8-azabicyclo[3.2.1]octan-8-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole 4-toluenesulfonate

Melting point 207.2-208.0°C (decomposition).

Example 1513

2-Methyl-6-nitro-2-[4-(4-trifluoromethoxyphenoxy)-benzyloxymethyl]-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 107.9-109.3°C.

Example 1514

6-Nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole

Melting point 173.2-177.3°C.

Example 1515

2-Methyl-6-nitro-2-{4-[4-(4-chlorophenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole

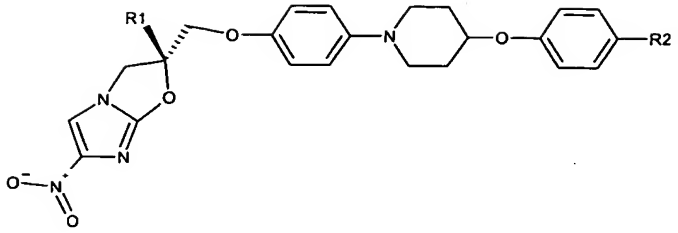
Melting point 151.0-152.3°C.

Example 1516

(S)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxy-phenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole

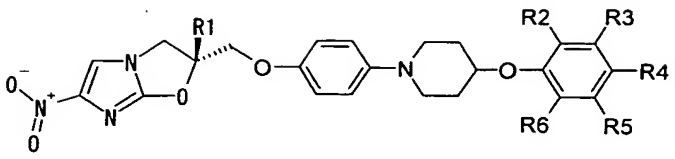
Melting point 199.0-200.5°C.

Table 91



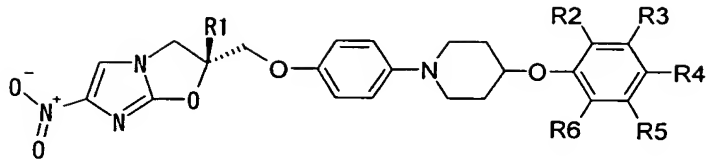
Example	R1	R2	mp (°C)
1517	$-CH_3$	-Cl	183.8 - 184
1518	$-CH_3$	$-CF_3$	179.4 - 180.9
1519	$-CH_3$	-F	190.2 - 192.8
1520	$-CH_3$	$-OCH_3$	193.3 - 194.5
1521	$-CH_3$	$-CH_3$	198.2 - 201.1 dec
1522	$-CH_3$	-H	194.5 - 197.5
1523	$-CH_3$	-CN	196.2 - 198.5 dec
1524	-H	$-OCF_3$	157.0 - 160.0
1525	-H	-Cl	166.5 - 171.0 dec

Table 92



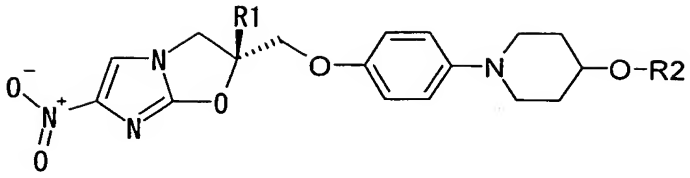
Example	R1	R2	R3	R4	R5	R6	MS (M+1)
1526	$-CH_3$	$-OCH_3$	-H	-H	-H	-H	481
1527	$-CH_3$	-H	$-OCH_3$	-H	-H	-H	481
1528	$-CH_3$	-H	-H	$-OCH_3$	-H	-H	481
1529	$-CH_3$	-H	-H	-H	$-OCH_3$	$-OCH_3$	511
1530	$-CH_3$	$-OCH_3$	-H	-H	-H	$-OCH_3$	511
1531	$-CH_3$	-H	-H	$-OCH_3$	$-OCH_3$	-H	511
1532	$-CH_3$	-H	$-OCH_3$	-H	$-OCH_3$	-H	511
1533	$-CH_3$	-H	-H	-H	-H	-H	451
1534	$-CH_3$	-H	-H	-H	-H	-Cl	485
1535	$-CH_3$	-H	-H	-H	-Cl	-H	485
1536	$-CH_3$	-H	-H	-Cl	-H	-H	485
1537	$-CH_3$	-Cl	-Cl	-H	-H	-H	519
1538	$-CH_3$	-Cl	-H	-Cl	-H	-H	519
1539	$-CH_3$	-Cl	-H	-H	-Cl	-H	519
1540	$-CH_3$	-Cl	-H	-H	-H	-Cl	519
1541	$-CH_3$	-H	-Cl	-Cl	-H	-H	519
1542	$-CH_3$	-H	-Cl	-H	-Cl	-H	519
1543	$-CH_3$	-H	-H	-H	-H	$-CH_3$	465
1544	$-CH_3$	-H	-H	-H	$-CH_3$	-H	465
1545	$-CH_3$	-H	-H	$-CH_3$	-H	-H	465
1546	$-CH_3$	$-CH_3$	$-CH_3$	-H	-H	-H	479
1547	$-CH_3$	$-CH_3$	-H	$-CH_3$	-H	-H	479
1548	$-CH_3$	$-CH_3$	-H	-H	$-CH_3$	-H	479
1549	$-CH_3$	$-CH_3$	-H	-H	-H	$-CH_3$	479
1550	$-CH_3$	-H	$-CH_3$	$-CH_3$	-H	-H	479
1551	$-CH_3$	-H	$-CH_3$	-H	$-CH_3$	-H	479
1552	$-CH_3$	-H	-H	-H	-H	-F	469
1553	$-CH_3$	-H	-H	-H	-F	-H	469
1554	$-CH_3$	-H	-H	-F	-H	-H	469
1555	$-CH_3$	-F	-F	-H	-H	-H	487
1556	$-CH_3$	-F	-H	-F	-H	-H	487
1557	$-CH_3$	-F	-H	-H	-F	-H	487
1558	$-CH_3$	-F	-H	-H	-H	-F	487
1559	$-CH_3$	-H	-F	-F	-H	-H	487
1560	$-CH_3$	$-CO_2C_2H_5$	-H	-H	-H	-H	523
1561	$-CH_3$	-H	$-CO_2C_2H_5$	-H	-H	-H	523
1562	$-CH_3$	-H	-H	$-CO_2C_2H_5$	-H	-H	523
1563	$-CH_3$	-CN	-H	-H	-H	-H	476
1564	$-CH_3$	-H	-CN	-H	-H	-H	476
1565	$-CH_3$	-H	-H	-CN	-H	-H	476
1566	$-CH_3$	-H	-H	-H	-H	$-CF_3$	519
1567	$-CH_3$	-H	-H	-H	$-CF_3$	-H	519

Table 93



Example	R1	R2	R3	R4	R5	R6	MS (M+1)
1568	$-CH_3$	-H	-H	$-CF_3$	-H	-H	519
1569	$-CH_3$	-H	-H	-H	-H	$-OCF_3$	535
1570	$-CH_3$	-H	-F	-H	-F	-H	487
1571	$-CH_3$	-H	-H	-H	$-OCF_3$	-H	535
1572	$-CH_3$	-H	-H	$-OCF_3$	-H	-H	535
1573	$-CH_3$	-H	-H	-H	-H	$-OCH(CH_3)_2$	509
1574	$-CH_3$	-H	-H	$-CH_3$	-H	$-CO_2C_2H_5$	537
1575	$-CH_3$	-H	-H	$-OCH_3$	-H	$-CO_2CH_3$	539
1576	$-CH_3$	-H	-H	-Br	-H	-F	547
1577	$-CH_3$	-H	$-CH_3$	-H	-H	-F	483
1578	$-CH_3$	-H	-H	-C3H7	-H	-H	493
1579	$-CH_3$	-H	-H	-Cl	-F	-H	503
1580	$-CH_3$	-H	-H	$-NO_2$	-H	-F	514
1581	$-CH_3$	-H	-H	$-CH_2CH=CH_2$	-H	$-OCH_3$	521
1582	$-CH_3$	-H	-H	-H	$-C_6H_5$	-H	527
1583	$-CH_3$	-H	-H	-H	$-N(C_2H_5)_2$	-H	522
1584	$-CH_3$	-H	$-CH=CHCH_3$ (cis)	-H	-H	$-OC_2H_5$	535
1585	$-CH_3$	-H	-H	$-CH(CH_3)_2$	-H	-H	493
1586	$-CH_3$	-H	-H	-H	$-NHCONH_2$	-H	509
1587	$-CH_3$	-H	-H	$-CH_2CH_2COCH_3$	-H	-H	521
1588	$-CH_3$	-H	-H	-H	$-NHC_6H_5$	-H	542
1589	$-CH_3$	-H	-H	$-NH_2$	-H	-Cl	500
1590	$-CH_3$	-H	-H	$-CH_2CO_2CH_3$	-H	-H	523
1591	$-CH_3$	-H	-H	$-OCH_3$	-H	-Cl	515
1592	$-CH_3$	-H	-H	-H	$-CO_2CH_3$	-H	509
1593	$-CH_3$	-H	-H	$-COCH_3$	-H	$-CONH_2$	536
1594	$-CH_3$	-H	-H	$-COC_2H_5$	-H	-H	507
1595	$-CH_3$	-H	-H	$-COCH_3$	-H	$-CH_3$	507
1596	$-CH_3$	-H	-H	$-COCH_3$	-OH	-H	509
1597	$-CH_3$	-H	-H	$-NHCOCH_3$	-H	-H	508
1598	$-CH_3$	-H	$-CH_3$	$-CH_3$	$-CH_3$	-H	493
1599	$-CH_3$	-H	-H	-H	-H	$-CH_2C_6H_5$	541
1600	$-CH_3$	-H	$-OCH_3$	-H	-H	$-CO_2CH_3$	539
1601	$-CH_3$	-H	-H	$-SCH_3$	-H	-H	497
1602	$-CH_3$	-H	-H	$-CHF_2$	-H	-H	517

Table 94



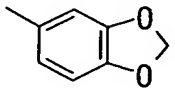
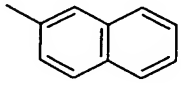
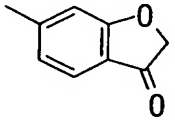
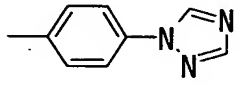
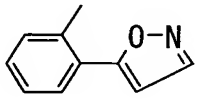
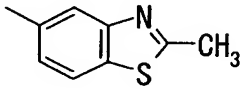
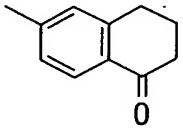
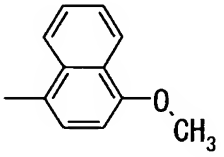
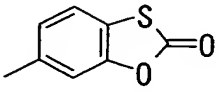
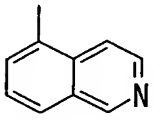
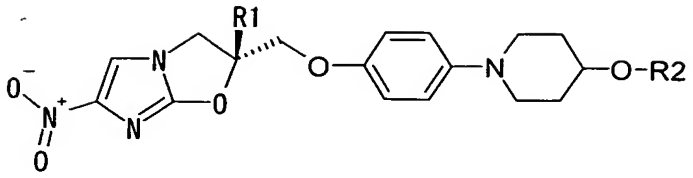
Example	R1	R2	MS (M+1)
1603	$-CH_3$		495
1604	$-CH_3$		501
1605	$-CH_3$		507
1606	$-CH_3$		518
1607	$-CH_3$		518
1608	$-CH_3$		522
1609	$-CH_3$		519
1610	$-CH_3$		531
1611	$-CH_3$		525
1612	$-CH_3$		502

Table 95



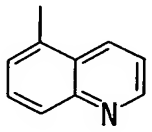
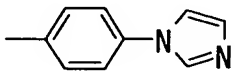
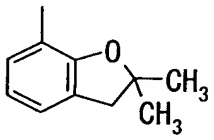
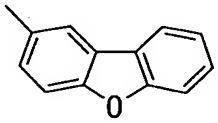
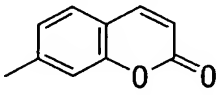
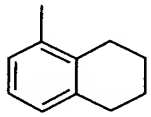
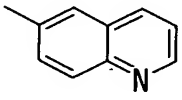
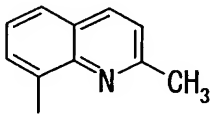
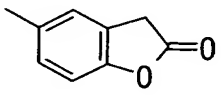
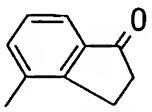
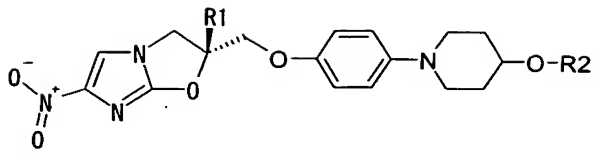
Example	R1	R2	MS(M+1)
1613	$-CH_3$		502
1614	$-CH_3$		517
1615	$-CH_3$		521
1616	$-CH_3$		541
1617	$-CH_3$		519
1618	$-CH_3$		505
1619	$-CH_3$		502
1620	$-CH_3$		516
1621	$-CH_3$		507
1622	$-CH_3$		505

Table 96



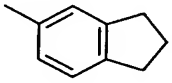
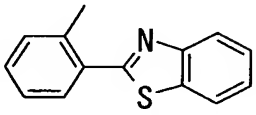
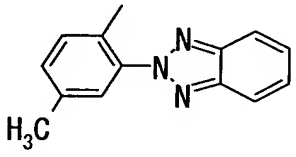
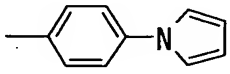
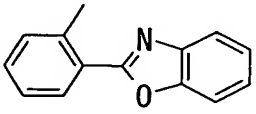
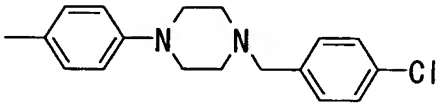
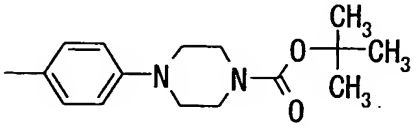
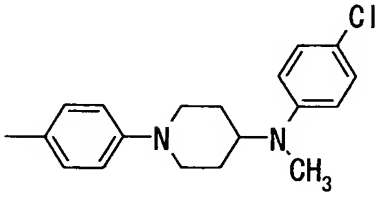
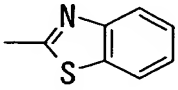
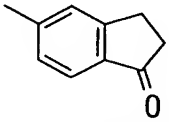
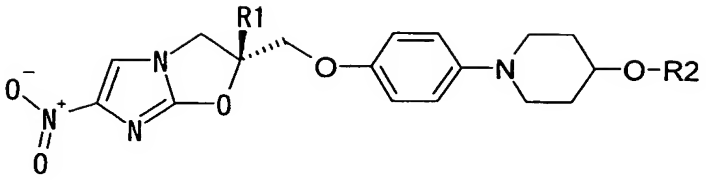
Example	R1	R2	MS(M+1)
1623	$-CH_3$		491
1624	$-CH_3$		584
1625	$-CH_3$		582
1626	$-CH_3$		516
1627	$-CH_3$		568
1628	$-CH_3$		659
1629	$-CH_3$		635
1630	$-CH_3$		673
1631	$-CH_3$		508
1632	$-CH_3$		505

Table 97



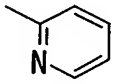
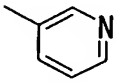
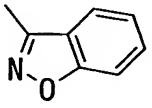
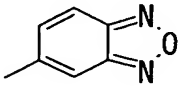
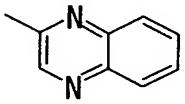
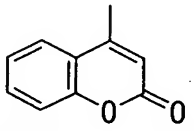
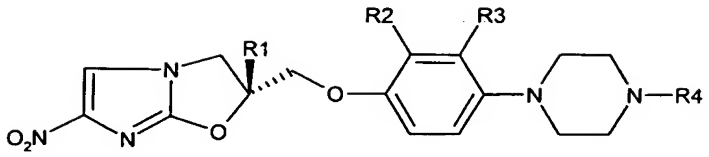
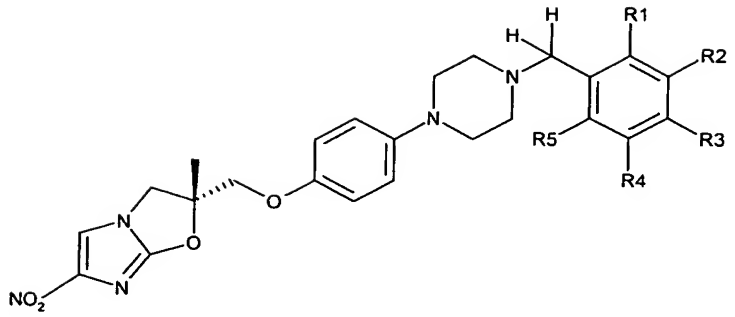
Example	R1	R2	MS(M+1)
1633	$-CH_3$		452
1634	$-CH_3$		452
1635	$-CH_3$		492
1636	$-CH_3$		493
1637	$-CH_3$		503
1638	$-CH_3$		

Table 98



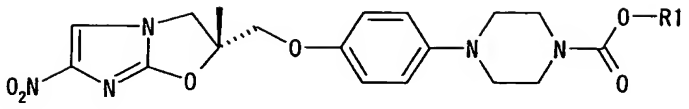
Example	R1	R2	R3	R4	mp(°C) or ^{1}H NMR
1639	$-CH_3$	-H	-H	$-CH_2C_6H_5$	208 - 210.5
1640	$-CH_3$	-H	-H	4-BrPhCH_2-	213.5 - 215.4
1641	$-CH_3$	-H	-H	4-BrPhCH_2OCO-	185.4 - 188.5
1642	$-CH_3$	-H	-H	-cyclo-C_6H_{11}	255.4 - 257.9 dec
1643	$-CH_3$	-H	-H	4-CF_3PhCH=N-	178.0 - 278.6
1644	$-CH_3$	-H	-H	4-CF_3OPhOCO-	226.5-226.8
1645	$-CH_3$	-H	-H	4-CF_3PhCCCH_2OCO-	186.4-187.7
1646	-H	-H	-H	4-CF_3OPh-	232.0 - 234.5
1647	-H	-H	-H	4-CF_3OPhCH_2-	171.4 - 172.9
1648	-H	-H	-H	4-ClPhCH_2-	191.2-192.0
1649	-H	-H	-H	$(CH_3)_3$COCO-	^{1}H NMR ($CDCl_3$) δ 1.48(9H, s), 2.99-3.04(4H, m), 3.55-3.60(4H, m), 4.22-4.37(2H, m), 4.39-4.49(2H, m), 5.56-5.63(1H, m), 6.79-6.91(4H , m), 7.63(1H , s).

Table 99



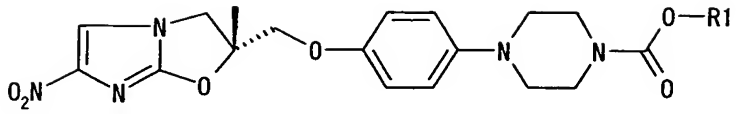
Example	R1	R2	R3	R4	R5	MS(M+1)
1650	-H	$-CF_3$	-H	-H	-H	518
1651	-H	-H	$-NO_2$	-H	-H	495
1652	-H	-H	$-CF_3$	-H	-H	518
1653	-H	-H	$-CH_3$	-H	-H	464
1654	-H	-H	-CN	-H	-H	475
1655	-H	-H	$-C_6H_5$	-H	-H	526
1656	-H	-H	-F	-H	-H	468
1657	-H	-Cl	-Cl	-H	-H	518
1658	$-CF_3$	-H	-H	-H	-H	518
1659	-H	-H	$-OCH_3$	-H	-H	480
1660	-H	-H	$-SCH_3$	-H	-H	496
1661	-H	-H	$-SO_2CH_3$	-H	-H	528
1662	-H	-H	$-OCH_2C_6H_5$	-H	-H	556
1663	-H	-Cl	-H	-Cl	-H	518
1664	-F	-F	-F	-H	-H	504
1665	-H	-H	$-OCOCH_3$	-H	-H	508

Table 100



Example	R1	MS(M+1)
1666	4-CF_3OPh-	564
1667	4-CH_3OPhCH_2-	524
1668	4-CH_3PhCH_2-	508
1669	4-$CH_3O_2CPhCH_2$-	552
1670	-$CH_2C_6H_5$	494
1671	4-CH_3SPhCH_2-	540
1672	4-NO_2PhCH_2-	539
1673	3,4,5-$(CH_3O)_3PhCH_2$-	584
1674	2-$CH_3CONHPhCH_2$-	551
1675	4-$FPhCH_2$-	512
1676	4-CF_3OPhCH_2-	578
1677	4-$PhCH_2OPhCH_2$-	600
1678	4-CF_3SPhCH_2-	594
1679	3-CF_3OPhCH_2-	578
1680	2-CF_3OPhCH_2-	578
1681	$C_6F_5CH_2$-	584
1682	$PhCH=CHCH_2$-	520
1683	4-$ClPhCH=CHCH_2$-	554
1684	4-$CF_3OPhCH=CHCH_2$-	604
1685	-$(CH_2)_2C_6H_5$	508
1686	$Ph(CH_2)_3$-	522
1687	$PhCCCH_2$-	518
1688	$PhS(CH_2)_2$-	540
1689	$PhCH_2O(CH_2)_2$-	538
1690	-$CH_2CH_2CH=CH_2$	458
1691	-CH_2CH_2CN	457
1692	CH_3 $(CH_2)_{15}$-	628
1693	$CH_3CH_2O(CH_2)_2O(CH_2)_2$-	520
1694	-CH_2CH_2CCH	456
1695	$CF_3CF_2CF_2CH_2$-	586
1696	-CH_2-cyclo-C_3H_5	458

Table 101



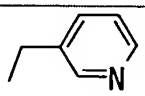
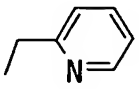
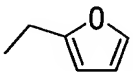
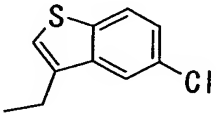
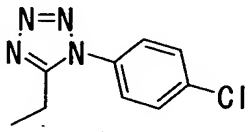
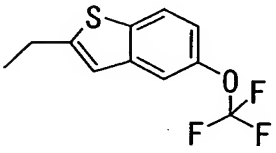
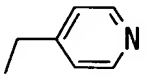
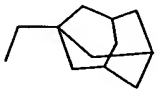
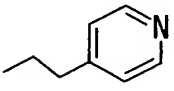
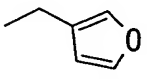
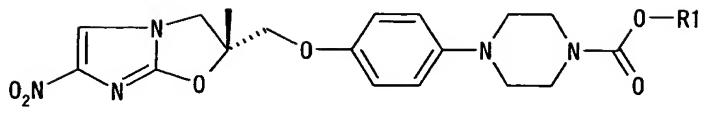
Example	R1	MS(M+1)
1697		495
1698		495
1699		484
1700		584
1701		596
1702		634
1703		495
1704		552
1705		509
1706		484

Table 102



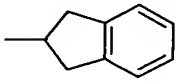
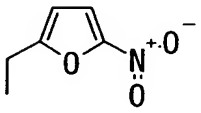
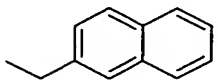
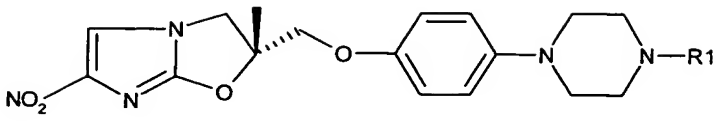
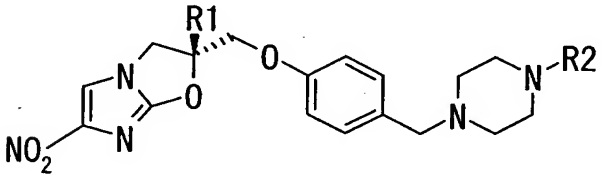
Example	R1	MS(M+1)
1707		520
1708		529
1709		544

Table 103



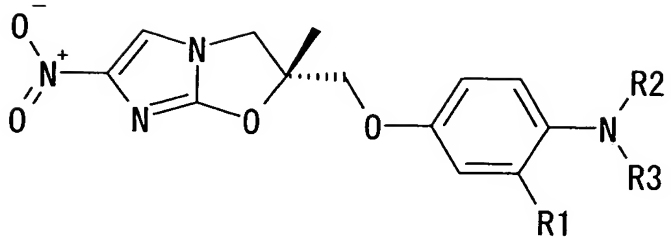
Example	R1	MS(M+1)
1710	$-CH_2CH=CH_2$	400
1711	$-C_6H_{13}$	444
1712	$-CH_2CN$	399
1713	$-(CH_2)_2CH(CH_3)_2$	430
1714	$-CH_2CON(CH_3)_2$	445

Table 104



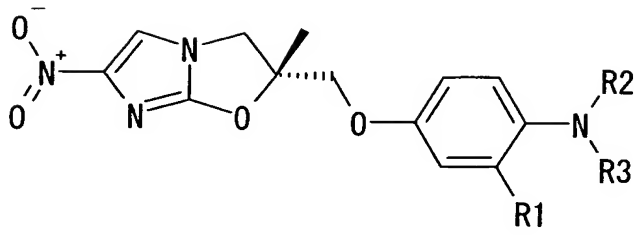
Example	R1	R2	mp(°C) or ^{1}H NMR
1715	$-CH_3$	$4-CF_3OPh-$	157.9 - 158.8
1716	$-CH_3$	$4-CF_3OPhCH_2-$	188.4 - 190.2
1717	$-CH_3$	$4-CF_3OPhCH_2OCO-$	112.1 - 115.4
1718	$-CH_3$	$4-CF_3OPhCO-$	
1719	$-CH_3$	$4-CF_3OPhNHCO-$	

Table 105



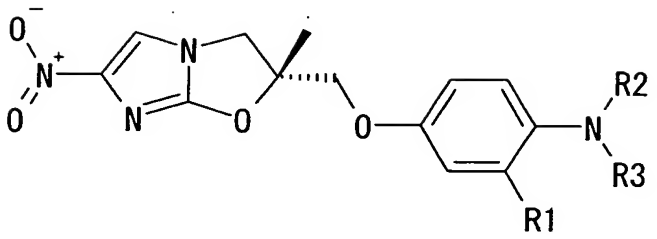
Example	R1	R2	R3	mp(°C)
1720	-H	4-CF_3OPh-	$-CH_3$	126.9-128.9
1721	-H	4-CF_3OPh-	$-C_2H_5$	102.1 - 103.1
1722	-H	4-ClPh-	$-C_2H_5$	121.7 - 123.6
1723	-H	$-C_6H_5$	$-CH_3$	169.5 - 171.0
1724	-H	4-CF_3OPhCH_2-	$-CH_3$	134.8 - 136.8
1725	-H	4-$ClPhCH_2$-	$-CH_3$	161.4 - 164.1
1726	-H	4-CF_3PhCH_2-	$-CH_3$	136.4 - 137.9
1727	-H	4-CF_3OPhCH_2-	$-C_2H_5$	119 - 120.5
1728	-H	4-CF_3PhCH_2-	$-C_2H_5$	134.3 - 135.7
1729	-H	4-$ClPhCH_2$-	$-C_2H_5$	135.8 - 137
1730	-F	4-CF_3OPhCH_2-	$-CH_3$	132.7 - 134.7
1731	-H	4-CF_3OPhCH_2-	4-CF_3OPhCH_2-	135.9 - 137
1732	-H	4-CF_3OPhCH_2-	$-C_6H_5$	198.9 - 200.8
1733	-H	4-CF_3PhCH_2-	$-C_6H_5$	192.7 - 194.7
1734	-H	4-$ClPhCH_2$-	$-C_6H_5$	195.1 - 196.1
1735	-H	$-C_6H_5$	$-COCH_3$	167.7 - 168.7
1736	-H	4-ClPh-	$-COCH_3$	220.0 - 223.5
1737	-H	4-CF_3Ph-	$-COCH_3$	223.1 - 224.6
1738	-H	4-CF_3OPh-	$-COCH_3$	243.6 - 244.9
1739	-F	4-ClPh-	$-COCH_3$	221.8 - 223.0
1740	-F	4-CF_3OPh-	$-COCH_3$	240.3 - 242.9
1741	-H	$-C_6H_5$	$-CO_2CH_3$	182.7 - 184.8
1742	-H	4-ClPh-	$-CO_2CH_3$	244.0 - 245.1
1743	-H	4-CF_3OPhCH_2-	-H	151.4 - 154.3
1744	-H	4-CF_3OPhCH_2-	$-CO_2C_2H_5$	105.1 - 107.6
1745	-H	4-$ClPh(CH_2)_2$-	$-CH_3$	116.1 - 117.6
1746	-H	4-$CF_3OPhO(CH_2)_3$-	-H	189.9 - 191.0
1747	-H	4-CF_3OPhCO-	$-CH_3$	143.3 - 145.9

Table 106



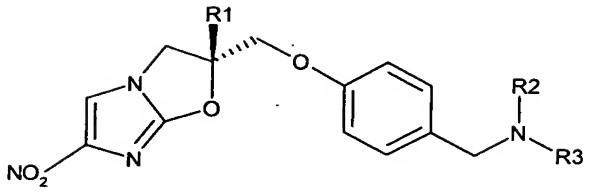
Example	R1	R2	R3	^{1}H NMR
1748	-H	4-CF_3Ph-	-CH_3	^{1}H NMR($CDCl_3$) δ 1.80(3H,s),3.28(3H,s),4.06(1H, d,J=10.2Hz),4.11(1H,d,J=10.2Hz),4.26(1H, d, J=10.2Hz), 4.52(1H, d, J=10.2Hz), 6.70(2H, d, J=8.7Hz), 6.88(2H, d, J=8.8Hz), 7.13(2H, d, J=8.8Hz), 7.39(2H, d, J=8.7Hz), 7.57(1H, s).
1749	-H	4-ClPh-	-CH_3	^{1}H NMR($CDCl_3$) δ 1.79(3H, s), 3.22(3H, s), 4.04(1H, d, J=10.4Hz), 4.08(1H, d, J=10.4Hz), 4.23(1H, d, J=10.1Hz), 4.50(1H, d, J=10.1Hz), 6.70-6.73(2H, m), 6.81-6.84(2H, m), 7.03-7.06(2H, m), 7.12-7.15(2H, m), 7.56(1H, s).
1750	-H	4-CF_3Ph-	-C_2H_5	^{1}H NMR($CDCl_3$) δ 1.20(3H, d, J=7.1Hz), 1.81(3H, s), 3.71(2H, q, J=7.1Hz), 4.07(1H, d, J=10.2Hz), 4.11(1H, d, J=10.2Hz), 4.27(1H, d, J=10.2Hz), 4.52(1H, d, J=10.2Hz), 6.63-6.66(2H, m), 6.88-6.91(2H, m), 7.10-7.12(2H, m), 7.34-7.37(2H, m), 7.57(1H, s).
1751	-F	4-ClPh-	-CH_3	^{1}H NMR($CDCl_3$) δ 1.80(3H, s), 3.20(3H, s), 4.06(1H, d, J=10.2Hz), 4.09(1H, d, J=10.1Hz), 4.25(1H, d, J=10.1Hz), 4.49(1H, d, J=10.2Hz), 6.54-6.57(2H, m), 6.64-6.71(2H, m), 7.09-7.19(3H, m), 7.57(1H, s).
1752	-H	4-CF_3OPhCH_2-	-$COCH_3$	^{1}H NMR($CDCl_3$) δ 1.79(3H, s), 1.85(3H, s), 4.06(1H, d, J=10.2Hz), 4.08(1H, d, J=10.2Hz), 4.24(1H, d, J=10.2Hz), 4.48(1H, d, J=10.2Hz), 4.82(2H, s), 6.78-6.82(2H, m), 6.88-6.91(2H, m), 7.09-7.11(2H, m), 7.20-7.22(2H, m), 7.56(1H, s).
1753	-H	4-CF_3OPhCO-	-CH_3	^{1}H NMR($CDCl_3$) δ 1.76(3H, s), 3.45(3H, s), 4.03(1H, d, J=10.1Hz), 4.04(1H, d, J=10.2Hz), 4.18(1H, d, J=10.1Hz), 4.46(1H, d, J=10.2Hz), 6.69-6.72(2H, m), 6.95-6.98(2H, m), 7.37-7.46(4H, m), 7.55(1H, s).
1754	-H	4-ClPhCO-	-CH_3	^{1}H NMR($CDCl_3$) δ 1.77(3H, s), 3.43(3H, s), 4.03(1H, d, J=10.1Hz), 4.04(1H, d, J=10.2Hz), 4.18(1H, d, J=10.1Hz), 4.46(1H, d, J=10.2Hz), 6.69-6.72(2H, m), 6.94-6.97(2H, m), 7.13-7.23(4H, m), 7.55(1H, s).
1755	-H	4-ClPhCO-	-H	^{1}H NMR(DMSO) δ 1.68(3H, s), 4.17-4.20(1H, m), 4.22-4.30(2H, m), 4.36-4.39(1H, m), 6.88-6.91(2H, m), 7.57-7.66(4H, m), 7.94-7.97(2H, m), 8.15(1H, s), 10.19(1H, brs).

Table 107



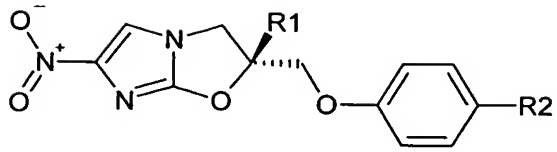
Example	R1	R2	R3	^{1}H NMR
1756	-H	4-ClPhCO-	-H	^{1}H NMR(DMSO) δ 1.68(3H,s), 4.17-4.20(1H, m), 4.22-4.30(2H, m), 4.36-4.39(1H, m), 6.88-6.91(2H, m), 7.57-7.66(4H, m), 7.94-7.97(2H, m), 8.15(1H, s), 10.19(1H, brs).
1757	-H	4-CF_3PhCO-	-H	^{1}H NMR(DMSO) δ 1.68(3H, s), 4.17-4.21(1H, m), 4.24-4.30(2H, m), 4.36-4.40(1H, m), 6.90-6.93(2H, m), 7.65-7.68(2H, m), 7.88-7.90(2H, m), 8.11-8.13(2H, m), 8.16(1H, s), 10.35(1H, brs).
1758	-H	4-CF_3OPhCO-	-H	^{1}H NMR(DMSO) δ 1.68(3H, s), 4.17-4.20(1H, m), 4.24-4.31(2H, m), 4.36-4.40(1H, m), 6.89-6.92(2H, m), 7.49-7.52(2H, m), 7.63-7.66(2H, m), 8.04-8.06(2H, m), 8.16(1H, s), 10.23(1H, brs).
1759	-H	4-ClPh-	-H	142.6 - 144.7
1760	-H	4-CF_3OPh$(CH_2)_2$-	-H	
1761	-H	4-CF_3OPh$(CH_2)_2$-	$-CH_3$	
1762	-H	4-CF_3OPhO$(CH_2)_3$-	$-C_2H_5$	107.6 - 109.2
1763	-H	4-CF_3OPhCOCH_2-	-H	
1764	-H	4-CF_3OPhCOCH_2-	$-CH_3$	

Table 108



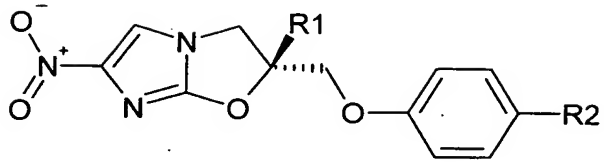
Example	R1	R2	R3	mp(°C) or ^{1}H NMR
1765	$-CH_3$	-H	4-ClPh-	171.5 - 173.5
1766	$-CH_3$	-H	4-CF_3Ph-	172.2 - 174.9
1767	$-CH_3$	$-CH_3$	4-CF_3OPhCH_2-	138.5 - 141.0
1768	$-CH_3$	-H	4-CF_3OPh-	165.1 - 167.2
1769	$-CH_3$	$-COCH_3$	4-CF_3OPh-	128.4 - 130.8
1770	$-CH_3$	$-CH_3$	4-CF_3OPh-	113.6 - 114.5
1771	$-CH_3$	$-CH_3$	4-CF_3Ph-	168.2 - 170.7
1772	$-CH_3$	$-COCH_3$	4-CF_3Ph-	132.8 - 133.9
1773	$-CH_3$	$-CH_3$	4-ClPh-	160.9 - 163.4
1774	$-CH_3$	$-CO_2C_2H_5$	4-CF_3OPh-	^{1}H NMR($CDCl_3$) δ 1.21(3H, t, d=7.1), 1.77(3H, s), 4.05(1H, d, J=10.3Hz), 4.06(1H, d, J=10.2Hz), 4.15-4.22(3H, m), 4.49(1H, d, J=10.3Hz), 4.78(2H, s), 6.74-6.78(2H, m), 7.07-7.13(6H, m), 7.55(1H, s).
1775	$-CH_3$	$-COCH_3$	4-ClPh-	^{1}H NMR($CDCl_3$) δ 1.78(3H, s), 1.86(3H, s), 4.03(1H, d, J=10.2Hz), 4.05(1H, d, J=10.1Hz), 4.21(1H, d, J=10.1Hz), 4.48(1H, d, J=10.2Hz), 4.78(2H, s), 6.71-6.74(2H, m), 6.87-6.89(2H, m), 7.08-7.11(2H, m), 7.28-7.32(2H, m), 7.55(1H, s).

Table 109



Example	R1	R2	mp(°C)
1776	$-CH_3$	-4-PYRIDYL	228.2 - 229.8 dec
1777	$-CH_3$	-CHO	176.0 - 179.5
1778	$-CH_3$	4-ClPhCO-	186.2 - 188.5
1779	$-CH_3$	4-CF_3PhCO-	170.3 - 172.4
1780	$-CH_3$	4-CF_3OPhCO-	159.7 - 160.7

Table 110



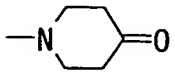
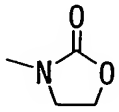
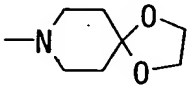
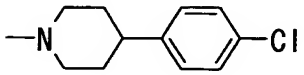
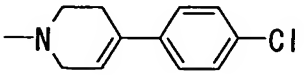
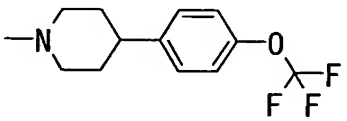
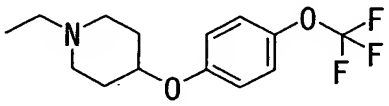
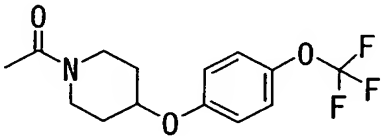
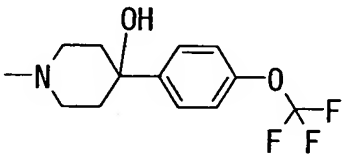
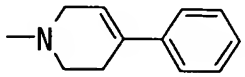
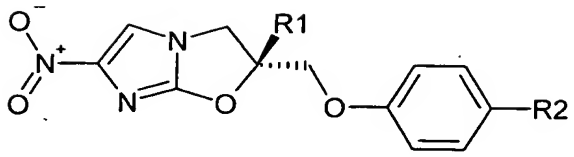
Example	R1	R2	mp(°C) or ^{1}H NMR
1781	$-CH_3$		177.4 - 184.3
1782	$-CH_3$		196.3 - 197.8
1783	$-CH_3$		212.3 - 214.0
1784	$-CH_3$		251.9 - 253.0
1785	$-CH_3$		216.7 - 219.5 dec
1786	$-CH_3$		248.1 - 248.2
1787	$-CH_3$		150.3 - 154.9
1788	$-CH_3$		150.8 - 151.2
1789	$-CH_3$		^{1}H NMR($CDCl_3$) δ 1.55(1H, s),1.60 (1H, s), 1.77(3H, s), 1.80-1.95(2H, m), 2.15-2.40(2H, m), 3.04-3.27(2H, m),3. 33-3.53(2H, m), 3.95-4.11(2H, m),4.19 (1H, d, J=10.2Hz), 4.50(1H, d,J=10.2 Hz), 6.71-6.86(2H, m), 6.88-7.02(2H, m), 7.14-7.31(2H, m), 7.47-7.63(3H, m).
1790	$-CH_3$		^{1}H NMR(DMSO) δ 1.67(3H, s),2.61(2H, brs), 3.74(2H, d, J=2.9Hz), .17(1H, d, J=13.0Hz), 4.21(2H, s), 6.28(1H, s), 6.81(2H, d, J=9.1Hz), 6.94(2H, d,J= 9.2Hz), 7.18-7.57(5H, m), 8.17(1H, s).

Table 111



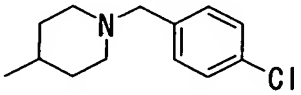
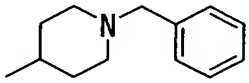
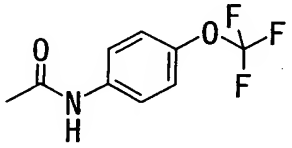
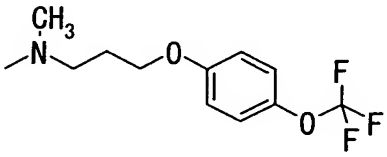
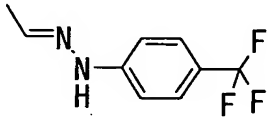
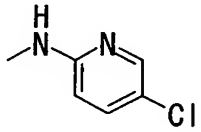
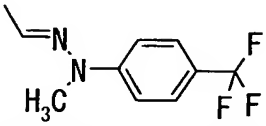
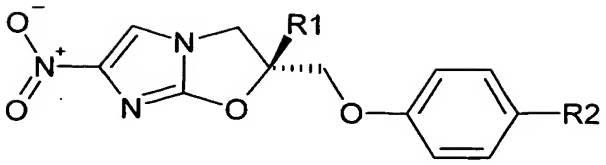
Example	R1	R2	mp(°C) or ^{1}H NMR
1791	$-CH_3$		202.0 - 203.5
1792	$-CH_3$		206.0
1793	$-CH_3$		247.8 - 249.8
1794	$-CH_3$		97.7 - 99.7
1795	$-CH_3$		172.5 - 175.8
1796	$-CH_3$		160.7 - 163.0
1797	$-CH_3$		^{1}H NMR($CDCl_3$) δ 1.81(3H, s), 3.44 (3H, s), 4.06(1H, d, J=10.24Hz), 4.12(1H, d, J=10.0Hz), 4.27(1H, d, J=10.0Hz), 4.52(1H, d, J=10.2Hz), 6.83-6.91(2H, m), 7.39-7.45(2H, m), 7.51-7.56(3H, m), 7.57(1H, s), 7.62-7.68(2H, m)

Table 112



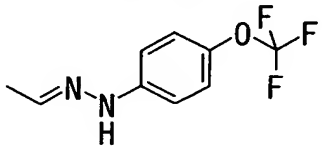
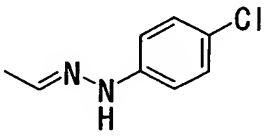
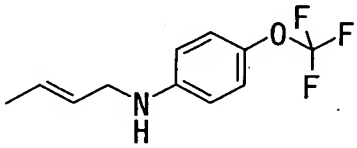
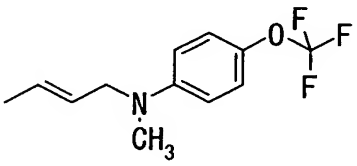
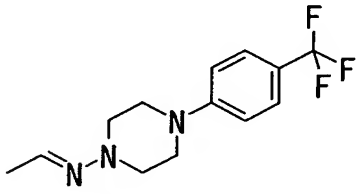
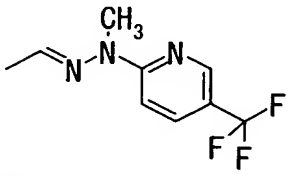
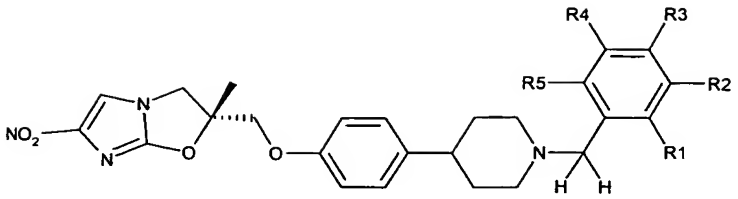
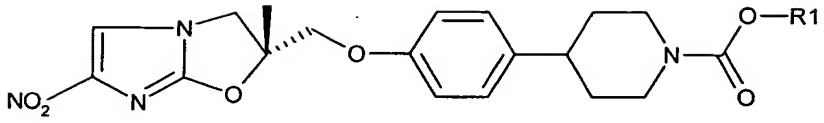
Example	R1	R2	mp(°C) or ^{1}H NMR
1798	$-CH_3$		^{1}H NMR($CDCl_3$) δ 1.80(3H, s), 4.01-4.14 (2H, m), 4.26(1H, d, J=10.0Hz), 4.51(1H, d, J=10.3Hz), 6.85(2H, d, J=8.6Hz), 7.03-7.09(4H, m), 7.53-7.60 (4H, m), 7.66(1H, s)
1799	$-CH_3$		^{1}H NMR($CDCl_3$) δ 1.81(3H, s), 4.05(1H, d, J=10.3Hz), 4.11(1H, d, J=10.0Hz), 4.26(1H, d, J=10.0Hz), 4.51(1H, d, J=10.3Hz), 6.83-7.05(4H, m), 7.20-7.26 (2H, m), 7.51-7.60(4H, m), 7.65(1H, s)
1800	$-CH_3$		
1801	$-CH_3$		
1802	$-CH_3$		
1803	$-CH_3$		209.1 - 212.9

Table 113



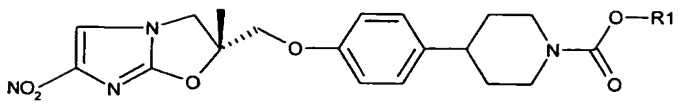
Example	R1	R2	R3	R4	R5	MS(M+1)
1804	-H	$-CF_3$	-H	-H	-H	517
1805	-H	-H	$-NO_2$	-H	-H	494
1806	-H	-H	$-CF_3$	-H	-H	517
1807	-H	-H	$-CH_3$	-H	-H	463
1808	-H	-H	-CN	-H	-H	474
1809	-H	-H	$-C_6H_5$	-H	-H	525
1810	-H	-H	-F	-H	-H	467
1811	-H	-Cl	-Cl	-H	-H	517
1812	$-CF_3$	-H	-H	-H	-H	517
1813	-H	-H	$-OCH_3$	-H	-H	479
1814	-H	-H	$-SCH_3$	-H	-H	495
1815	-H	-H	$-SO_2CH_3$	-H	-H	527
1816	-H	-H	$-OCH_2C_6H_5$	-H	-H	555
1817	-H	-Cl	-H	-Cl	-H	517
1818	-F	-F	-F	-H	-H	503
1819	-H	-H	$-OCOCH_3$	-H	-H	507

Table 114



Example	R1	MS(M+1)
1820	4-CF_3OPh-	563
1821	4-CH_3OPhCH_2-	523
1822	4-CH_3PhCH_2-	507
1823	4-$CH_3O_2CPhCH_2$-	551
1824	-$CH_2C_6H_5$	493
1825	4-CH_3SPhCH_2-	539
1826	4-NO_2PhCH_2-	538
1827	3,4,5-$(CH_3O)_3PhCH_2$-	583
1828	2-$CH_3CONHPhCH_2$-	550
1829	4-$FPhCH_2$-	511
1830	4-CF_3OPhCH_2-	577
1831	4-$PhCH_2OPhCH_2$-	599
1832	4-CF_3SPhCH_2-	593
1833	3-CF_3OPhCH_2-	577
1834	2-CF_3OPhCH_2-	577
1835	$C_6F_5CH_2$-	583
1836	$PhCH=CHCH_2$-	519
1837	4-$ClPhCH=CHCH_2$-	553
1838	4-$CF_3OPhCH=CHCH_2$-	603
1839	-$(CH_2)_2C_6H_5$	507
1840	$Ph(CH_2)_3$-	521
1841	$PhCCCH_2$-	517
1842	$PhS(CH_2)_2$-	539
1843	$PhCH_2O(CH_2)_2$-	537
1844	-$CH_2CH_2CH=CH_2$	457
1845	-CH_2CH_2CN	456
1846	$CH_3CH_2O(CH_2)_2O(CH_2)_2$-	519
1847	-CH_2CH_2CCH	455
1848	$CF_3CF_2CF_2CH_2$-	585
1849	-CH_2-cyclo-C_3H_5	457

Table 115



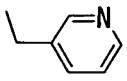
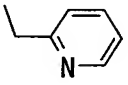
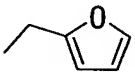
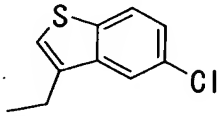
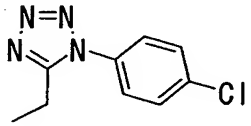
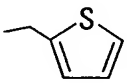
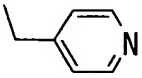
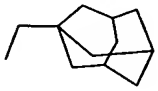
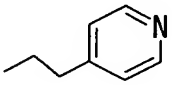
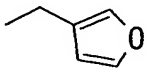
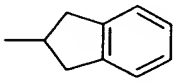
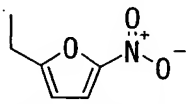
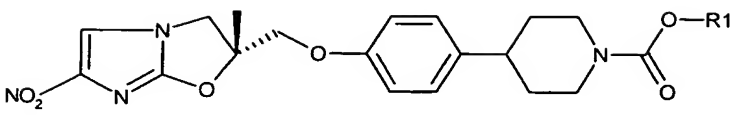
Example	R1	MS(M+1)
1850		494
1851		494
1852		483
1853		583
1854		595
1855		499
1856		494
1857		551
1858		508
1859		483
1860		519
1861		528

Table 116



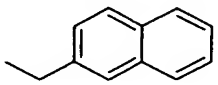
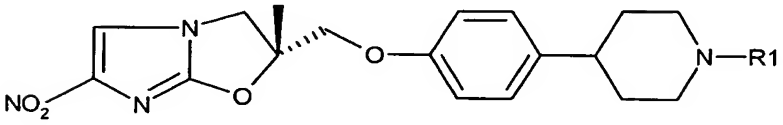
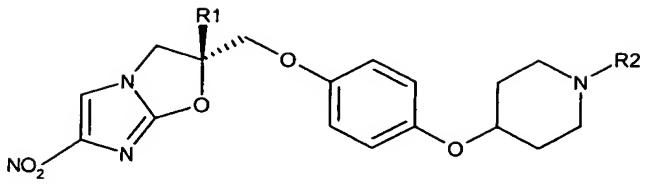
Example	R1	MS(M+1)
1862		543

Table 117



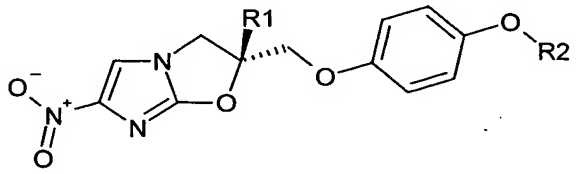
Example	R1	MS(M+1)
1863	$-CH_2CH=CH_2$	399
1864	$-(CH_2)_2C_6H_5$	463
1865	$-C_6H_{13}$	443
1866	$-CH_2CN$	398
1867	$-CH_2CON(CH_3)_2$	444
1868	$PhCOCH_2-$	477

Table 118



Example	R1	R2	mp (°C)
1869	$-CH_3$	4-CF_3PhCH_2-	171.4 - 172.4
1870	$-CH_3$	4-CF_3PhCH_2OCO-	130.4 - 131.7
1871	$-CH_3$	4-$ClPhCH_2OCO$-	126.8 - 129.1
1872	$-CH_3$	4-CF_3OPhCH_2OCO-	143.8 - 144.8
1873	$-CH_3$	4-$ClPhCH_2$-	183.0 - 187.2
1874	$-CH_3$	4-CF_3OPhCH_2-	174.3 - 176.5
1875	$-CH_3$	4-CF_3Ph-	156.7 - 157.7
1876	$-CH_3$	$(CH_3)_3COCO$-	197.0 - 198.2
1877	$-CH_3$	4-CF_3OPh-	154.5 - 156.7

Table 119



Example	R1	R2	mp (°C) or ^1H NMR
1878	$-CH_3$	4-$ClPhCH_2$-	214.3 - 216.1
1879	$-CH_3$	4-CF_3Ph-	158.5 - 160.1
1880	$-CH_3$	4-CF_3OPh-	161.7 - 164.4
1881	$-CH_3$	4-ClPh-	163.5 - 166.3
1882	$-CH_3$	4-CF_3OPhCH_2-	^1H NMR($CDCl_3$) δ 1.76(3H, s), 4.02(1H, d, J=10.2Hz), 4.04(1H, d, J=10.2Hz), 4.18(1H, d, J=10.2Hz), 4.48(1H, d, J=10.2Hz), 5.00(2H, s), 6.77-6.81(2H, m), 6.85-6.90(2H, m), 7.21-7.23 (2H, m), 7.42-7.45(2H, m), 7.54(1H, s).
1883	$-CH_3$	4-CF_3PhCH_2-	^1H NMR($CDCl_3$) δ 1.77(3H, s), 4.02(1H, d, J=10.2Hz), 4.04(1H, d, J=10.2Hz), 4.18(1H, d, J=10.2Hz), 4.49(1H, d, J=10.2Hz), 5.07(2H, s), 6.77-6.81(2H, m), 6.85-6.91(2H, m), 7.51-7.55 (3H, m), 7.62-7.65(2H, m).

Example 1884

Production of (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole

4-[4-(4-Trifluoromethoxyphenoxy)piperidin-1-yl]phenol (693 mg, 1.96 mmol) was dissolved in N,N'-dimethylformamide (3 ml), and sodium hydride (86 mg, 2.16 mmol) was added while cooling on ice followed by stirring at 70-75°C for 20 minutes. The mixture was cooled on ice. To the solution, a solution prepared by dissolving (R)-2-bromo-4-nitro-1-(2-methyl-2-oxiranylmethyl)imidazole (720 mg, 2.75 mmol) in N,N'-dimethylformamide (3 ml) was added followed by stirring at 70-75°C for 20 minutes. The reaction mixture was allowed to return to room temperature, ice water (25 ml) was added, and the resultant solution was extracted with methylene chloride (50 ml) three times. The organic phases were combined, washed with water 3 times, and dried over magnesium sulfate. After filtration, the filtrate was concentrated, and the residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 3/1). Recrystallization from ethyl acetate/isopropyl ether gave (R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole (343 mg, 33%) as a light yellow powder.

Example 1885

(1) Production of 3-(4-trifluoromethylphenyl)-2-

propenyl (S)-4-[3-(2-bromo-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-carboxylate

A mixture of (R)-2-bromo-4-nitro-1-(2-methyl-2-oxiranylmethyl)imidazole (2.04 g, 7.78 mmol), 3-(4-trifluoromethylphenyl)-2-propenyl piperazine-1-carboxylate (2.69 g, 8.56 mmol) and N,N'-dimethylformamide (10 ml) was stirred at 50°C for 20 hours. The reaction solution was allowed to return to room temperature, water was added, and the resultant solution was extracted with ethyl acetate (15 ml) twice. The organic phases were combined, washed with water three times, and dried over sodium sulfate. After filtration, the filtrate was concentrated, and the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/2) to obtain 3-(4-trifluoromethylphenyl)-2-propenyl (S)-4-[3-(2-bromo-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazin-1-carboxylate (3.77 g, 84%) as a yellow oil.

^{1}H-NMR (CDCl3) δppm:

1.16 (3H, s), 2.36 (1H, d, J = 14.0 Hz), 2.43 - 2.76 (5H, m), 3.21 (1H, s), 3.41 - 3.57 (4H, m), 4.01 (2H, s), 4.78 (2H, dd, J = 1.0 Hz, 6.1 Hz), 6.29 - 6.43 (1H, m), 6.66 (1H, d, J = 16.0 Hz), 7.48 (2H, d, J = 8.3 Hz), 7.58 (2H, d, J = 8.3 Hz), 8.10 (1H, s).

(2) Production of 3-(4-trifluoromethylphenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate

3-(4-Trifluoromethylphenyl)-2-propenyl (S)-4-

[3-(2-bromo-4-nitroimidazol-1-yl)-2-hydroxy-2-methylpropyl]piperazine-1-carboxylate (3.5 g, 6.07 mmol) was dissolved in N,N'-dimethylformamide (10.5 ml), and sodium hydride (316 mg, 7.89 mmol) was added while cooling on ice followed by stirring at the same temperature for 1.5 hours. To the reaction solution, ethyl acetate (3.5 ml) and water (24.5 ml) were added followed by stirring for 30 minutes. The precipitated crystals were filtered off, washed with water, and purified by silica gel column chromatography (ethyl acetate). Recrystallization from 2-propanol/water gives a light yellow powder of 3-(4-trifluoromethyl-phenyl)-2-propenyl (S)-4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethyl)piperazine-1-carboxylate (2.07 g, 69%).

Test example 1

Antimicrobial assay (agar dilution method)

The minimal inhibitory concentration of the 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound obtained in Example 397 against Mycobacterium tuberculosis (M. tuberculosis H37Rv) was determined using a 7H11 medium (manufactured by BBL). The above strain had been cultured on a 7H9 medium (manufactured by BBL) in advance, the number of viable cells had been counted, and a cell suspension with the final viable cell count approximately 10^6 CFU/ml was prepared, using a cell suspension stored freezing at -80°C. 5 μl of the

thus prepared cell suspension was inoculated onto the 7H11 agar medium containing the test compound and then cultured at 37°C for 14 days. Thereafter, the culture was subjected to the test to determine the minimal inhibitory concentration.

The minimal inhibitory concentration of the compound against M. tuberculosis H37Rv was 0.024 μg/ml.